Acute Coronary Syndromes in the Maastricht area : acute myocardial infarction, unstable angina pectoris, sudden cardiac arrest

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Acute Myocardial Infarction
Unstable Angina Pectoris
Sudden Cardiac Arrest

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Aan alle hartpatiënten waarvan
gegevens gebruikt werden voor
de totstandkoming van dit proefschrift

CONTENTS

CHAPTER 1

Introduction

INTRODUCTION

Coronary heart disease (CHD) is a common disease in the industrialized world. The clinical manifestations may vary widely from silent ischemia, stable angina pectoris, unstable angina pectoris (UAP), acute myocardial infarction (MI), cardiac failure, cardiac arrhythmias, atrioventricular conduction defects and sudden cardiac arrest (SCA). The most common acute expressions of CHD are acute MI, UAP and SCA.

Aims of both studies

During the past 25 years, mortality from CHD has been decreasing (Chapter 2). To make correct decisions about the incorporation, expansion or limitation of preventive and curative measures, it is important to study the causes of the decrease in mortality. One reason could be a decrease in the incidence of CHD, possibly due to changes in CHD risk factors and in lifestyle in the general population. Another explanation could be a more benign course of CHD and a third reason a decrease in short- and long-term mortality of patients with CHD due to better treatment.
This latter hypothesis is subject of part one of this thesis. Many randomized controlled clinical studies have shown that the advent of new treatment strategies such as thrombolytic agents, balloon angioplasty and coronary bypass grafting improved prognosis in selected patients. Also the introduction of new and better drugs has resulted in a better outcome. To investigate whether these new treatments result in a decreased mortality and morbidity in unselected patients, a study was performed including all patients with acute MI and UAP admitted to the University Hospital of Maastricht in 1982, 1988 and 1994. This study focuses on the changes in in-hospital (Chapter 3), short- (Chapter 4) and long-term (Chapter 5) mortality after acute MI and UAP (Chapter 6) and relates baseline variables, clinical variables and treatment to the outcome in terms of mortality and morbidity. In contrast to patients admitted in 1982 those seen in 1988 and 1994 were treated with the newly available drugs such as thrombolytics and ACE inhibitors, catheter interventions and cardiac surgery. In these three patient groups the data of in-hospital and long-term (1 and 5 years) mortality and morbidity were compared.
Finally we studied a subgroup of patients in whom the initial diagnosis was UAP but where MI was diagnosed after subsequent evaluation (Chapter 7).

Yearly many sudden cardiac deaths occur outside the hospital making it an important public health problem. In the Netherlands the exact incidence of sudden cardiac death is unknown. To develop primary and secondary prevention measures it is therefore useful to perform an epidemiologic study

in which the incidence, circumstances, causes and survival of SCA and the characteristics and risk factors of victims are evaluated.
The purpose of the second part of this thesis was to describe the incidence and survival rates of SCA in the region of Maastricht in the Netherlands (chapter 8). The possible contribution of alcohol and coffee consumption to SCA in patients with CHD is not known which was reason to study the risk of these life-style factors and classical CHD risk factors (such as smoking, hypertension, hypercholesterolemia and diabetes mellitus) on SCA in patients with CHD (chapter 9). To get more insight into the underlying mechanisms of SCA, chapter 10 reports on autopsy data of SCA victims. This part of the study focuses on causes of SCA and differences in chronic and acute cardiac abnormalities between SCA victims with and without a previous cardiac history. Studies on the etiology of SCA in cardiac arrest survivors are contradictory. Chapter 11 reports on causes of SCA in cardiac arrest survivors and on factors which influence the resuscitation success rate.

In this introduction we will review insights as to the incidence, risk factors, pathology and treatment of acute MI, UAP and SCA. Subsequently we will describe demographic characteristics of the study area.

Acute myocardial infarction / Unstable angina pectoris

Incidence

In many industrialized countries a trend is observed towards lower mortality rates from CHD (1,2). However, this disease still remains the most important cause of death despite all efforts that have been made during the past decades.
In the Netherlands with a total number of around 15 million inhabitants, approximately 25,000 suffer from acute MI yearly with one-fourth of all deaths being due to MI (3,4). More than 60 per cent of the deaths associated with MI occur within one hour of the event and are caused by arrhythmias, most often ventricular fibrillation (5). There is a gender difference in the incidence of CHD: the Framingham study reported that among persons between the age of 35 and 84 years men have about twice the total incidence of CHD mortality and morbidity of women. There is a difference of approximately 10 years between men and women in the appearance and peak incidence of CHD. However in contrast to men, women have higher fatality rates from coronary attacks (6). Although in recent years a lower CHD mortality rate has been observed in the overall population, there is an increase in the number of cases of CHD. This is accompanied by growing health care costs especially because of an increased ageing of the population; 80% of all deaths from CHD occur in people over 65 years of age (7).

Risk factors

Risk factors for CHD have been described in epidemiological studies starting with the Framingham study (8). The predisposing modifiable risk factors for coronary disease include hypertension, dyslipidemia (raised serum low density lipoprotein - low high density lipoprotein - elevated triglycerides), impaired glucose tolerance, physical inactivity, cigarette smoking, type A behavior and vital exhaustion (9,10). In addition there are non-modifiable risk factors such as age, gender and a family history of premature CHD. Most patients have a combination of risk factors with each factor multiplying the effects of the others (11). Moreover it has been demonstrated that certain risk factors such as elevated serum cholesterol levels, smoking and type A behavior appear to cluster in patients with hypertension (12,13). In addition to this, there is always the risk that treatment of one risk factor with a certain drug may act adversely by increasing the level or impact of another risk factor. For example the treatment of hypertension with B-blockers may have an adverse effect on serum cholesterol levels.
Finally, although much interest currently exists in the treatment of certain single risk factors such as by lipid lowering therapy, it should be realized that CHD risk is multifactorial; the risk associated with a given lipid value is modulated to a great extent by the presence of other factors.

Pathology

Almost all myocardial infarctions result from atherosclerosis of the coronary arteries, generally with superimposed thrombosis, leading to severe luminal narrowing or occlusion of a coronary artery and thereby reduction or interruption of the blood supply to a part of the myocardium. The size of the MI depends on a number of factors such as the location and the severity of the atherosclerotic lesion, the size of the vascular bed perfused, the time between occlusion and reperfusion of the coronary artery, the extent of development of collateral circulation (5). The infarction can be transmural, in which myocardial necrosis involves the full thickness of the ventricular wall, or subendocardial when necrosis involves the subendocardium, the intramural myocardium, or both without extending to the epicardium.
Unstable angina pectoris (UAP) is caused by either increased myocardial oxygen demand in the presence of severely restricted coronary reserve or by a dynamic stenosis caused by coronary vasoconstriction or both (14).
Patients with UAP have an increased risk to die suddenly, to have persistent angina or to develop an acute MI (15-17). The clinical presentation may be one of new onset angina, progressive angina, angina at rest, or persistent angina.

Treatment

Treatment for MI has changed during the past decade with the introduction of several new strategies having as a common goal to reopen the infarct vessel in order to decrease infarct size and preserve ventricular function. Furthermore in patients surviving the acute phase, treatment is directed towards prevention of future events and regression of coronary atherosclerosis.
After admission to the coronary care unit, initial treatment of MI consists of intravenous heparin, control of pain, anxiety and the reduction of ischemia by intravenously administered nitroglycerin (18,19). Beta-adrenoceptor blockers administered in the early hours of MI have shown to reduce ischemia especially in patients with sinus tachycardia or hypertension (20,21).
In the late 1980s and early 1990s treatment focused on early reperfusion of the infarct related artery with thrombolytic agents showing improvement in left ventricular function and reduction of mortality (22-27). Numerous reports have shown that the administration of thrombolytic agents in patients with acute MI results in a decreased early and long-term mortality together with limitation of the infarct size and a better left ventricular ejection fraction. A great deal of effort has been spent to identify new agents with a more specific action combined with fewer complications and these studies are still ongoing. It has also been shown that PTCA applied in the acute phase of MI without prior administration of thrombolytic agents results in an excellent early and late event-free survival (28-30).
The challenge is to individualize the treatment and to identify the high risk patient requiring more aggressive treatment (31-33). Mortality figures for medically treated patients vary significantly in studies performed in the past decade (34-39). A comparison of the effect of surgical versus medical therapy on mortality has resulted in conflicting results (40-45).
Coronary angioplasty in the setting of UAP is associated with a high success rate and improved prognosis (46,47).
Possibly related to the differences in results is the lack of uniformity in the definition of UAP. Therefore there is need for a generally accepted classification (48,49).

Sudden cardiac arrest

Incidence

Although a declining trend has been reported (50-53), SCA is still the most frequent cause of death in many countries. However, the exact incidence of SCA is not known. In the United States for instance, annual figures varied between 200,000 and 450,000 victims (54,55). Most recent studies report

300,000 victims annually which is about half of all cardiovascular deaths in the US (50).
The Framingham Heart study showed that the incidence of sudden cardiac death increases with age. It doubles with each decade of age, with women lagging behind men by 20 years (56,57). Furthermore, both in women and men with prior CHD, the incidence is 8 to 10 fold higher compared to the incidence in those not known with CHD (58).
Also in the Netherlands the exact incidence of sudden cardiac death is unknown. In a report written by the Council of Health on the epidemiology and prevention of CHD in the Netherlands in 1984 (59), it was mentioned that sudden death caused by circulatory arrest outside the hospital was one of the most important but at the same time the most neglected cause of death in our country.

Risk factors

A number of studies have shown that the classical risk factors for CHD such as age, hypertension, obesity, smoking, glucose intolerance, hypercholesterolemia and a positive family history are associated with an increased risk of SCA (60-63).
Persons with symptomatic CHD tend to have a higher chance of dying suddenly compared to those not known with CHD (58). In the Framingham study, the only positive predictors for sudden death in men with prior CHD were left ventricular hypertrophy (LVH) and intraventricular conduction disturbances. In women with CHD, only the hematocrit was predictive. Reasons for these differences between men and women are not clear (58).
Subsequently, in persons with a previous MI, several prognostic factors have been identified. These include specific electrocardiographic abnormalities, spontaneous sustained ventricular tachycardias and poor cardiac function. In short-term follow-up studies an ejection fraction equal to or less than 30% has been identified as the most powerful predictor for sudden cardiac death (64).
Next to clinical parameters, psycho-social factors also seem to influence the risk of SCA after MI. Social isolation and high levels of life-stress seem to predict a greater than four-fold increase in the risk of sudden death in men with previous MI (65). Also low educational level appears to increase the risk of sudden death after MI (66). This was also thought for type A personality, however recently the validity of the discrimination of high-risk subgroup based on type A personality characteristics has been challenged (67).
In patients with UAP who are at high risk for sudden cardiac death, the major risk factors include a large area of (reversible) ischemia on the myocardial scintigram, recurrent angina pectoris during hospitalization, significant ST-T changes caused by myocardial ischemia, congestive heart failure and cardiomegaly on chest x-ray examination (68).

The asymptomatic group dying suddenly is very difficult to identify prior to the event. In the Framingham study those patients showed the same incidence of classical risk factors as those developing CHD. A study by Rahe (69) showed a relation between the magnitude of recent life changes (health, work, home) and MI and sudden cardiac death (69). In a case-control study on sudden cardiac death in women, cases were less often married, had fewer children and had greater educational discrepancies with their spouses and had more often a history of psychiatric treatment, cigarette smoking and consumed greater quantities of alcohol than did age- related controls living in the same neighborhood (70).
A study by Golombeck and coworkers (71) showed that the vital exhaustion syndrome which is characterized as loss of energy/undue fatigue, increased irritability and feelings of demoralization, is also an independent risk indicator of sudden cardiac death in both persons with and without previous CHD.
Studies have also investigated alcohol and coffee consumption as risk factors for CHD and CHD mortality. Slight or moderate alcohol consumption appears to have a negative effect (72) while heavy alcohol intake is positively associated with CHD mortality and SCA (73). Consumption of coffee has shown a positive association with the serum cholesterol concentration (74). However, a meta-analysis on the effect of coffee on MI and death from CHD showed discrepancies between several studies (75).

Pathology

The many different causes of sudden death may be divided into cardiac and non-cardiac. Examples of the latter are pulmonary embolism and other vascular diseases such as aortic dissection or rupture (76).
In the majority of victims the underlying cause is cardiac and in this category coronary artery disease is most common. Other cardiac causes include aortic stenosis, hypertrophic cardiomyopathy, dilated cardiomyopathy, right ventricular dysplasia, mitral valve prolapse, prolonged QT syndrome, Wolf Parkinson White syndrome and drug induced ventricular arrhythmias (76,77).

The most common cardiac mechanism for sudden death is ventricular fibrillation (VF) with or without preceding ventricular tachycardia (VT) (78). In 1889, MacWilliam was the first to consider that sudden cardiac death in humans was due to VF (79). This hypothesis was based on experiments in animals. Until that time, it was assumed that sudden death or 'cardiac failure' as it was than commonly called, was due to a sudden cessation of the heart action in diastole. According to MacWilliam, the predisposing anatomic substrate for VF was an atherosclerotic lesion in the coronary artery or degenerative changes in the muscular walls or the valves (79).

Clinical and pathological studies indicate that sudden death in CHD is due either to a ventricular arrhythmia arising within a scarred and hypertrophied left ventricle or an acute ischemic event (80). The interaction between chronic structural abnormalities and functional modulations may lead to ectopic ventricular rhythms and VT/VF (81, 82).
Pathological findings in sudden coronary death victims include 1. chronic and 2. acute lesions in the coronary arteries and 3. chronic and 4. acute lesions in the myocardium (81).
1. Chronic atherosclerotic lesions are a common pathological finding in coronary arteries of sudden coronary death victims (83).
2. The acute lesion is usually a rupture of a chronic atherosclerotic lesion (a plaque) followed by thrombotic deposits (84,85).
Plaques which are prone to rupture often contain high concentrations of cholesterol esters and their shape is often eccentric. Plaque rupture is thought to be caused by different factors: 1. A sudden change in blood pressure and vessel lumen as a result of acute systemic hypertension or local spasm. 2. Factors which weaken the structure of the plaque such as hyperlipidemia, high plasma levels of nicotine and angiotensine, circulating immune complexes and molecular changes in the collagen structure of the fibrous cap. 3. Capillary bleeding: bleeding of the vasa vasorum coming from the adventitia entering the plaque (86,87,88).
A chronically developing severe stenosis of a coronary artery can lead to the development of collateral arteries. Asymptomatic persons with plaque rupture and no collateral circulation may have a higher chance of dying suddenly in case of a sudden occlusion of the coronary artery compared to those in whom collateral circulation has developed (89-92).
3/4. LVH has been identified as an independent risk factor for lethal arrhythmias (93). Many patients with coronary artery disease who die suddenly have secondary ventricular hypertrophy due to associated hypertension or in conjunction with extensive coronary artery disease (83). Chronic LVH causes focal fibrosis and regional variations in action potential characteristics making the patient more susceptible to VF during acute ischemia (94). Also tissue that has healed after a MI is susceptible to the electrically destabilizing effect of acute ischemia (95).

Treatment

In the past, various techniques to rescue the apparently dying SCA victim have been described and applied. Nowadays, the treatment and management of the cardiac arrest victims outside hospital, can be summarized in the so called 'Chain of survival' concept which can be divided into four steps: 1. the initial response, 2. basic life support, 3. defibrillation and 4. advanced life support (96,97).

When a person collapses, the first step of the witness or bystander is to confirm that the collapse is due to cardiac arrest and to activate the emergency medical service. Absence of the carotid or femoral pulse is the primary diagnostic criterion (97). The second step is the immediate application of basic life support to maintain viability of the brain, heart and other vital organs through mouth to mouth breathing and chest compression.
Several studies have shown that the immediate start of basic cardiopulmonary resuscitation (CPR) after recognition of a SCA is essential for survival (98,99).
The last two steps in the 'Chain of survival' are early ventricular defibrillation and early advanced life support. The development of human resuscitation by cardiac massage and defibrillation by Kouwenhoven and Zoll has been a major advance in clinical cardiology (100). Rapid conversion to an effective cardiac rhythm is a key step for successful resuscitation (101). The goal of advanced life support is to optimize ventilation by intubation, to change the cardiac rhythm into one which is hemodynamically effective and to maintain and support the restored circulation by intravenous administration of medications.

Study area and organization of emergency care

The study was conducted at the academic hospital of Maastricht in the Netherlands. This is the only hospital in a well defined area and serves this area as a primary hospital for acute ischemic heart disease. This area encloses 203 square kilometers and has approximately 182,000 inhabitants of whom around 133,000 (73%) are between the age of 20 and 75 years. The age distribution of the Maastricht population is shown in figure 1.
The hospital has a 24 hours service for acute referrals from about 100 general practitioners situated in the region. Patients can also present to the first heart aid of the hospital without referral by a physician.
In the area there is one emergency medical service (EMS) which has seven ambulances. All seven ambulances are equipped with defibrillators, material for intubation and oxygen administration and medication like adrenaline, atropine, lidocaine and procainamide. The EMS system can be contacted 24 hours a day by calling 112. Each ambulance has one nurse and one driver.

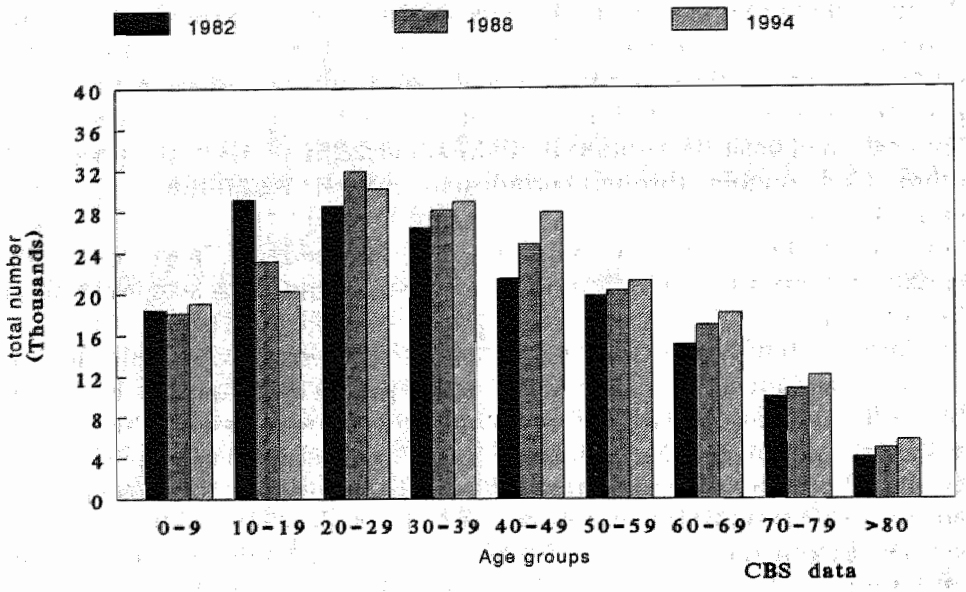

Figure 1. Age distribution of inhabitants of the region of Maastricht for the years 1982, 1988 and 1994.

References

1. O'Rourke RA. Overview of trends in heart disease. Changing prognosis after myocardial infarction. Ann Epidemiol 1993;3:541-6.
2. Uemura K, Pisa Z. Trends in cardiovascular disease mortality in industrialized countries since 1950. World Health Stat Q 1988;41:155-178.
3. Ruwaard D, Kramers PGN. Volksgezondheid Toekomst Verkenning. De gezondheidstoestand van de Nederlandse bevolking in de periode 1950-2010. Rijksinstituut voor volksgezondheid en Milieuhygiëne. Den Haag, 1993.
4. Hart en vaatziekten in Nederland 1995. Cijfers over ziekte en sterfte Nederlandse Hartstichting. Gegevens van het Centraal Bureau voor de Statistiek, SIG Zorginformatie en het Rijksinstituut voor de volksgezondheid en milieuhygiëne. Den Haag, 1995.
5. Pasternak RC, Braunwald E, Sobel BE. Acute myocardial infarction. In: Heart disease. A textbook of cardiovascular medicine. Third edition. Philadelphia: WB Saunders 1992:1200-91.
6. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26 year follow-up of the Framingham population. Am Heart J 1986;11:383-90.
7. Weijenberg MP. Prospective studies on coronary heart disease in the elderly. The role of classical and new risk factors. Landbouwuniversiteit Wageningen 1996 (thesis).

8. Kannel WB, Gordon T. The Framingham Study: An epidemiological investigation of cardiovascular disease, section 30. Some characteristics related to the incidence of cardiovascular disease and death: the Framingham study. 18- year follow-up. Washington, D.C., Dept. of Health, Education, and Welfare: Publication No.(NIH) 1974:574-99.
9. Kannel WB, Vokonas PS. Demographics of the prevalence, incidence, and management of coronary heart disease in the elderly and in women. Ann Epidemiol 1992;2:5-14.
10. Appels A, Schouten E. Burnout as a risk factor for coronary heart disease. J Behav Med 1991;17:53-9.
11. Silberberg JS. Estimating the benefits of cholesterol lowering: Are risk factors for coronary heart disease multiplicative? J Clin Epidemiol 1990;43:875-9.
12. Irvine J, Garner DM, Craig HM, Logan AG. Prevalence of type A behavior in untreated hypertensive individuals. Hypertension 1991;18:72-8.
13. Poulter N, Management of multiple risk factors for coronary heart disease in patients with hypertension. Am Heart J 1991;121:246-50.
14. Maseri A. Pathogenetic classifications of unstable angina as a guideline to individual patient management and prognosis. Am J Med 1986;80(suppl 4c):48-55.
15. Falk E. Unstable angina with fatal outcome: Dynamic coronary thrombosis leading to infarction and/or sudden death. Circulation 1985;71:699-708.
16. Fischl SJ, Herman MV, Gorlin R. The intermediate coronary syndrome: clinical, angiographic and therapeutic aspects. N Engl J Med 1973;288:1193-7.
17. Krauss KR, Hutter AM, De Sanctis RW. Acute coronary insufficiency; course and follow-up. Circulation 1972;45:66-70.
18. Derrida JP, Sal R, Chiche P. Favorable effects of prolonged nitroglycerin infusion in patients with acute myocardial infarction. Am Heart J 1978;63:615-8.
19. Mikolich JR, Nicoloff NB, Robinson PH, Logue HB. Relief of refractory angina with continuous intravenous infusion of nitroglycerin. Chest 1980;77:375-9.
20. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;27:335-71.
21. Richterova A, Herlitz J, Holmesberg S, Swedberg K, Waagstein F, Waldenstrom A, Vedin A, Wennerblom B, Wilhelmsson B, Hjalmarson A. Goteborg Metoprolol trial: effects on chest pain. Am J Cardiol 1984;53:32D-36D.
22. The Multicenter Postinfarction Research Group. Risk stratification and survival after acute myocardial infarction. N Engl J Med 1983;309:331-6.
23. Stadius ML, Davis K, Maymard C, Ritchie JL, Kennedy JW. Risk stratification for 1-year survival based on characteristics identified in the early hours for acute myocardial infarction. The Western Washington Intracoronary Streptokinase Trial. Circulation 1968;74:703-11.
24. Gruppo Italiano per lo Studio della Streptochinasi Nell' infarcto Myocardio (GISSI). Effectiveness of thrombolytic therapy. Lancet 1986;11:397-402.
25. Simoons ML, Serruys PW, Van der Brand M. et al. Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. J Am Coll Cardiol 1986;7:717-28.
26. Second International Study of Infarct Survival (ISIS-2) Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. J Am Coll Cardiol 1988;12:3A-13A.

27. Simoons ML, Vos J, Thijssen JPG, Vermeer F, Verheugt FWA, Krauss XH, Cats VM. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. J Am Coll Cardiol 1989;14:1609-15.
28. De Boer MJ, Suryapranata H, Hoorntje JCA, Reiffers S, Ay Lee Liem, Miedema K, Hermens WT, Van den Brand MJBM, Zijlstra F. Limitation of the infarct size and preservation of left ventricular function after primary coronary angioplasty compared with intravenous streptokinase in acute myocardial infarction. Circulation 1994;90:753-61.
29. Stone GW, Rutherford BD, McConahay DR, Johnson WL, Giorgi LV, Ligon RW, Hartzler GO. Direct coronary angioplasty in acute myocardial infarction: outcome in patients with one vessel disease. J Am Coll Cardiol 1990;15:534-43.
30. Stack RS, Califf RM, Hinohara T, Phillips HR, Pryor DB,Simonton CA, Carlson EB, Morris KG, Behar VS, Kong Y, Peter RH, Hlatky MA, O'Connor CM, Mark DB. Survival and cardiac event rates in the first year after emergency coronary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1988;11:1141-9.
31. Moss AJ. Profile of high risk in people known to have coronary heart disease; a review. Circulation 1975;52:suppl III:147-51.
32. Vlietstra RE, Assad Morell JL, Frye RLK, Elveback LR, Conolly DC, Ritman EL, Pluth JR, Barnhorst DA, Danielson GK, Wallace RB. Survival predictors in coronary artery disease: medical and surgical comparisons. Mayo Clin Proc 1977;52:85-9.
33. Ouyang P, Brinker JA, Mellits ED, Weisfeldt ML, Gerstenblith G. Variables predictive of successful medical therapy in patients with unstable angina: selection by multivariate analysis from clinical, electrocardiographic, and angiographic evaluations. Circulation 1984;70:367-76.
34. De Servi S, Berzuini C, Poma E, Ghio S, Scire A, Cioffi P, Ardissino D, Montemartini C, Specchia G. Long-term survival and risk stratification in patients with angina at rest undergoing medical treatment. Int J Cardiol 1989;22:43-50.
35. Severi S, Michelassi C, Orsini E, Marraccini P, L'Abbate A. Long-term prognosis of transient acute myocardial ischemia at rest. Am J Cardiol 1989;64:889-95.
36. Gazes P, Mobley EM, Faris HM, Duncan RC, Humphries GB. Preinfarctional (unstable) angina-a prospective study-ten year follow-up: prognostic significance of electrocardiographic changes. Circulation 1973;48:331-7.
37. Lewis HD, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE III, Schnaper HW, Lewinter MM, Linares E, Pouget JM, Sabharwal SC, Chesler E, DeMots H. Prospective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of Veterans Administration Cooperative Study. N Engl J Med 1983;309:396-403.
38. Graham I, Mulcahy R, Hickey N, O'Neill W, Daly L. Natural history of coronary heart disease: a study of 586 men surviving an initial acute attack. Am Heart J 1983;105:249-57.
39. Harris PJ, Lee KL, Harrel FE, Behar VS, Rosati RA. Outcome in medically treated coronary artery disease. Ischemic events: nonfatal infarction and death. Circulation 1980;62:718-26.
40. De Servi S, Berzuini C, Ghio S, Ferrario M, Poma E, Scire A, Ragni T, Vigano M, Montemartini C, Specchia G. Effects of surgical versus medical treatment on long-term prognosis in angina at rest: an observational non-randomized study of 400 patients. Eur Heart J 1988;9:513-9.
41. Hultgren HN, Pfeifer JF, Angell WW, Lipton MJ, Bilisoly J. Unstable angina: comparison of medical and surgical management. Am J Cardiol 1977;39:734-40.

42. Parisi AF, Khuri S, Deupree RH, Sharma GVRK, Scott SM, Luchi RJ. Medical compared with surgical management of unstable angina: 5-year mortality and morbidity in the veterans administration study. Circulation 1989;80:1176-88.
43. Unstable Angina Pectoris Study Group. Unstable angina pectoris: National Cooperative Study Group to Compare Surgical and Medical Therapy. I. Report of protocol and patient population. Am J Cardiol 1976;37:896-902.
44. Unstable Angina Pectoris Study Group. Unstable Angina Pectoris: National Cooperative Study Group to Compare Surgical and Medical Therapy. II. In-hospital experience and initial follow-up results in patients with one, two and three vessel disease. Am J Cardiol 1978;42:839-48.
45. Luchi RJ, Scott SM, Deupree RH, and the Principal Investigators and Their Associates of Veterans Administration Cooperative Study No. 28. Comparison of medical and surgical treatment for unstable angina pectoris. Results of a Veterans Administration Cooperative Study. N Engl J Med 1987;316:977-84.
46. De Feyter PJ, Serruys PW, vd Brand M, Hugenholtz PG. Percutaneous transluminal angioplasty for unstable angina. Am J Cardiol 1991;68:125B-135B.
47. De Feyter PJ, Suryapranata H, Serruys PW, Beat K, van Domburg R, vd Brand M, Tijssen JJ, Azar AJ, Hugenholtz PG. Coronary angioplasty for unstable angina: Immediate and late results in 200 consecutive patients with identification of risk factors for unfavorable early and late outcome. J Am Coll Cardiol 1988;12:324-33.
48. Braunwald E. Unstable angina: a classification. Circulation 1989;80:410-4.
49. Fowler NO. Preinfarctional angina; a need for an objective definition and for a controlled clinical trial of its management. Circulation 1971;44:755-9.
50. Gillum RF. Sudden coronary death in the United States 1980-1985. Circulation 1989;79:756-65.
51. Gordon T, Thom T. The recent decrease in CHD mortality. Prev Med 1975;4:115-25.
52. Kuller LH, Perper JA, Dai WS, et al: Sudden death and the decline in coronary heart disease mortality. J Chronic Dis 1986;39:1001-19.
53. Goldberg RJ. Declining out-of-hospital sudden coronary death rates. Additional pieces of the epidemiologic puzzle. Circulation 1989;79:1369-73.
54. Greene HL. Sudden arrhythmic cardiac death - Mechanisms, resuscitation and classification: the Seattle perspective. Am J Cardiol 1990;65:4B-12B.
55. Becker LB, Smith DW, Rhodes KV. Incidence of cardiac arrest: a neglected factor in evaluating survival rates. Ann Emerg Med 1993;22:86-91.
56. Kannel WB, McGee DL. Epidemiology of sudden death: insights from the Framingham study. Cardiovasc Clin 1985;15:93-105.
57. Kannel WB, McGee DL, Schatzkin A. An epidemiological perspective of sudden death. 26 Year follow-up in the Framingham study. Drugs 1984;28:1-16.
58. Schatzkin A, Cupples LA, Heeren T, et al. Sudden death in the Framingham Heart Study. Differences in incidence and risk factors by sex and coronary disease status. Am J Epidemiol 1984;120:888-99.
59. Commissie van de Gezondheidsraad. Gezondheidsraad advies inzake epidemiologie en preventie van ischemische hartziekten. No 1984/16, Den Haag, 29 juni 1984.
60. Suhonen O, Reunanen A, Knekt P, Aromaa A. Risk factors for sudden and non-sudden coronary death. Acta Med Scand 1988;223:19-25.
61. Doyle JT, Kannel WB, McNamara PM, Quickenton P, Gordon T. Factors related to suddenness of death from coronary disease: combined Albany-Framingham studies. Am J Cardiol 1976;37:1073-7.

62. Kannel WB, Doyle JT, McNamara PM, Quickenton P, Gordon T. Precursors of sudden coronary death. Factors related to the incidence of sudden death. Circulation 1975;51:606-13.
63. Kannel WB, Plehn JF, Cupples LA. Cardiac failure and sudden death in the Framingham study. Am Heart J 1988;115:869-75.
64. Bigger JT Jr, Fleiss JL, Kleiger R, et al. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation 1984;69:250-8.
65. Ruberman W, Weinblatt E, Goldberg JD, Chandhary BS. Psychosocial influences on mortality after myocardial infarction. N Engl J Med 1984;311:552-9.
66. Weinblatt E, Ruberman W, Goldberg JD, et al. Relation of education to sudden death after myocardial infarction. N Engl J Med 1978;299:60-5.
67. Shekelle RB, Gale M, Norusis M. Type A score (Jenkins Activity Survey) and risk of recurrent coronary heart disease in the aspirin myocardial infarction study. Am J Cardiol 1985;56:221-5.
68. Schroeder JS, Lamb IH, Harrison DC. Patients admitted to the coronary care unit for chest pain. High-risk subgroup for subsequent cardiovascular death. Am J Cardiol 1977;39:829-32.
69. Rahe RH, Romo M, Bennett L, Siltman P. Recent life changes, myocardial infarction and abrupt coronary death. Arch Intern Med 1974;133:221-5.
70. Talbott E, Kuller LH, Detre K, Perper J. Biologic and psychosocial risk factors of sudden death from coronary disease in white women. Am J Cardiol 1977;39:858-64.
71. Golombeck B, Appels A, van Breukelen G, de Vreede J, Gorgels A. Sudden cardiac death - predicted by vital exhaustion (submitted).
72. Moore RD, Pearson TA. Moderate alcohol consumption and coronary artery disease. A review. Medicine 1986;65:242-67.
73. Lithell H, Aberg H, Selinus I, Hedstrand H. Alcohol intemperance and sudden death. Br Med J 1987;294:1456-8.
74. Aro A. The effect of coffee on serum lipids and its clinical considerations. Cardiovasc Risk Factors 1993;3:238-43.
75. Greenland S. A meta-analysis of coffee, myocardial infarction and coronary death. Epidemiology 1993;4:366-74.
76. Sokolow M, McIlroy MB, Cheitlin MD. Clinical cardiology. Appleton and Lange, USA 1990.
77. Segal BL, Iskandrian AS, Kotler MN. Sudden cardiac death. in: Sudden cardiac death, J Morganroth, Horowitz LN. Orlando Grune and Stratton, US 1985.
78. Myerburg RJ, Conde CA, Sung RJ, et al. Clinical, electrophysiologic and hemodynamic profile of patients resuscitated from prehospital cardiac arrest. Am J Med 1980;68:568-76.
79. MacWilliam JA. Cardiac failure and sudden death. Br Med J 1889;1:6-8.
80. Davies MJ. A macro and micro view of coronary vascular insult in ischemic heart disease. Circulation 1990;82:38-46.
81. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: Structure, function, and time-dependence of risk. Circulation 1992;85:I2-I10.
82. Wellens HJJ, Brugada P. Sudden cardiac death: A multifactorial problem. In: Cardiac arrhythmias: Were to go from here? Brugada P, Wellens HJJ (eds), Futura Publishing Company. Mount Kisco, New York 1987.
83. Perper JA, Kuller LH, Cooper M. Atherosclerosis of coronary arteries in sudden unexpected deaths. Circulation 1975;52:27-33.

84. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the committee on vascular lesions of the council on arteriosclerosis, American Heart Association. Circulation 1995;92:1355-74.
85. Myerburg RJ, Kessler KM, Bassett AL, Castellanos A. A biological approach to sudden cardiac death: structure, function and cause. Am J Cardiol 1989;63:1512-16.
86. Fuster V., Stein B, Ambrose JA, Badimon L, Badimon JJ, Chesebro JH. Atherosclerotic plaque rupture and thrombosis. Evolving concepts. Circulation 1990;82:II47-II59.
87. Mustard JF, Packham MA, Kinlough-Rathbone RL. Platelets, bloodflow and the vessel wall. Circulation 1990;81:I24-I27.
88. Constantinides P. Cause of thrombosis in human atherosclerotic arteries. Am J of Cardiol 1990;66:37-40.
89. Virmani R, Roberts WC. Sudden cardiac death. Hum Pathol 1987;18:485-92.
90. Epstein SE, Quyyumi AA, Bonow RO. Possible mechanisms and implications for screening asymptomatic populations. N Engl J Med 1989;321:320-4.
91. Roberts WC. Sudden cardiac death: a diversity of causes with focus on atherosclerotic coronary artery disease. Am J Cardiol 1990;65:13B-19B.
92. Warnes CA, Roberts WC. Sudden coronary death: Relation of amount and distribution of coronary narrowing at necropsy to previous symptoms of myocardial ischemia, left ventricular scarring and heart weight. Am J Cardiol 1984;54:65-73.
93. Anderson KP. Sudden death, hypertension and hypertrophy. J Cardiovasc Pharmacol 1984;6:498-503.
94. Kohya T, Kimura S, Myerburg RJ, Bassett AL. Susceptibility of hypertrophied rat hearts to ventricular fibrillation during acute ischemia. J Mol Cell Cardiol 1988;20:159-68.
95. Myerburg RJ, Epstein K, Gaide MS, et al. Electrophysiologic consequences of experimental acute ischemia superimposed on healed myocardial infarction in cats. Am J Cardiol 1982;49:323-30.
96. Cummins RO, Ornato JP, Thies WH, et al. Improving survival from sudden cardiac arrest: The 'chain of survival' concept. A statement for health professionals from the advanced cardiac life support subcommittee and the emergency cardiac care committee, American Heart Association. Circulation 1991;83:1832-47.
97. Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. In:Braunwald E, (ed): Heart disease; A textbook of cardiovascular Medicine. Third edition. Philadelphia: WB Saunders 1992:756-89.
98. Baringer JR, Salzman EW, Jones WA, Friedlich AL. External cardiac message. N Engl J Med 1961;265:62-4.
99. Lowenstein SR, Sbyan EM, Lassen CF, Kenn DC. Benefits of training physicians in advanced cardiac life support. Chest 1986;89:512-7.
100. De Silva RA. John MacWilliam, evolutionary biology and sudden cardiac death. J Am Coll Cardiol 1989;14:1843-9.
101. Cobb LA, Hallstrom AP. Community based cardiopulmonary resuscitation: What have we learned? Ann NY Acad Sci 1982;382:330-5.

PART I

Acute Myocardial Infarction Unstable Angina Pectoris

CHAPTER 2

Did Prognosis After Acute Myocardial Infarction Change During the Past 30 Years?

A Meta - Analysis

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ABSTRACT

Much effort has been spent to improve survival after acute myocardial infarction. To investigate how effective this effort has been, a meta-analysis was performed of studies published between 1960 and 1987 concerning mortality after acute myocardial infarction.

Thirty six studies were analyzed. They were classified with respect to deaths in the hospital and at 1 month and the 5 year mortality rate starting at hospital discharge.

Mortality was assessed from all studies, by comparing studies from different institutions with use of identical inclusion criteria (externally controlled studies) and by analyzing studies reporting on changes in mortality in two or more comparable patient cohorts, admitted to the same institution at different time periods (internally controlled studies). Reports on clinical trials (for example thrombolytic therapy, beta-blockade) in acute myocardial infarction were excluded.

Average overall in-hospital mortality decreased from 29% during the 1960s to 21% during the 1970s and to 16% during the 1980s. The externally controlled studies also showed a declining trend: from 1960 to 1969, 32% from 1970 to 1979, 19% and from 1980 to 1987, 15%. The 1 month overall mortality rate decreased from 31% during the 1960s to 25% during the 1970s and 18% during the 1980s. Most internally controlled studies also showed significant improvement in in-hospital and 1 month survival. In contrast 5-years mortality after hospital discharge did not significantly decrease (33% from 1960 to 1969 and 33% from 1970 to 1979).

It is concluded that in the prethrombolytic era, short-term prognosis after acute myocardial infarction has improved since 1960. Changes in long-term prognosis after hospital discharge however could not be demonstrated. Information about the effect of thrombolytic therapy and early revascularization is urgently needed.

INTRODUCTION

Coronary artery disease is still the main cause of death in many parts of the world. Acute myocardial infarction accounts for 33% of the total mortality associated with coronary artery disease (1). Therefore much effort has been spent during the last decades to improve treatment of the acute and chronic phase of myocardial infarction and to prevent complications and recurrences. For this purpose, many new diagnostic, monitoring and treatment strategies have been developed, such as the coronary care unit (2), coronary angiography (3), coronary bypass surgery (4) percutaneous transluminal coronary angioplasty (5), hemodynamic monitoring (6) and treatment with intra-aortic balloon counterpulsation (7). In addition new drugs have been introduced such as beta blocking agents (8), calcium channel antagonists, angiotensin-converting enzyme inhibitors and agents influencing coagulation state and thrombus formation (for example coumarin derivatives (9) aspirin, (10) and fibrinolytic drugs (11,12)).
Improvement in prognosis has been shown after certain interventions in selected populations, for example the use of beta-blocker therapy (8) after acute myocardial infarction or the effect of fibrinolytic agents during the acute stage of infarction (10). It is also important to know whether prognosis has improved in unselected populations, because this more appropriately reflects the overall effects of improvement in treatment.
During the last decades, many studies reported on prognosis after acute myocardial infarction. Few, however, compared prognosis in different time periods. The time interval between different observations was frequently relatively short and never > 10 years. The question whether mortality rates after acute myocardial infarction have declined during the past 30 years can therefore only be answered by a meta-analysis.

METHODS

Meta-analysis

This technique of quantitative reviewing is thought to be an efficient way to summarize numerous published reports (13). Meta-analysis can give more insight and often makes it possible to reach stronger conclusions and bring effects into sharper focus. Meta-analysis is helpful in highlighting gaps in published studies, providing insight into new directions for research and finding mediating or interactional relations that cannot be hypothesized and tested in an individual study (13).

To search for studies concerning prognosis after myocardial infarction, we used the Medline database from the U.S. National Library of Medicine

(containing all volumes of Index Medicus, published between 1983 and 1988). The following key words were used: myocardial infarction, long-term prognosis, short-term prognosis, survival, mortality, case fatality, in-hospital mortality and 5-years mortality. By reviewing these references, we identified relevant studies published before 1983 to the present.
We included studies reporting on in-hospital, 1-month and 5-years mortality after acute myocardial infarction. Only one publication from investigators reporting data over the same period was included. Reports on clinical trials (for example, thrombolytic agents, beta-blockade) were excluded because such trials usually report on selected patient groups. Finally, studies performed before 1960 were excluded because during that period, enzymatic confirmation of myocardial infarction was not generally available.
From each publication the following information was collected: year of publication, design of the study, demographic and baseline characteristics of the study population, methods and results, site and time period during which the study was performed.
Studies were analyzed with regard to short- and long-term prognosis. Because short-term prognosis is reported as either in-hospital mortality or 1-month mortality after admission, the results of both types of studies were analyzed separately. Because 5-year survival rates are reported in most long-term follow-up studies, results of this follow-up period were pooled.
Studies were divided according to three time periods: 1960 to 1969, 1970 to 1979 and 1980 to 1987. The studies were analyzed in three ways: 1) overall mortality, and mortality assessed by 2) "externally controlled" studies and 3) "internally controlled" studies.

Overall mortality

To obtain global information on prognosis during these three periods, results of all studies were pooled. Studies were separately analyzed with regard to in-hospital, 1-month and 5-years mortality.

Externally controlled studies

Because results may be biased when data from studies with different inclusion criteria are compared, a subanalysis of studies was done by controlling for inclusion criteria.
We termed these reports "externally controlled studies". Included in this analysis were studies that met the following diagnostic criteria: 1) the presence of at least two of the following three criteria for myocardial infarction (typical chest pain, typical electrocardiographic (ECG) changes and typical serum enzyme elevations). Apart from these diagnostic criteria the following baseline criteria were used: no limitations according to 1) gender, 2) age, 3) infarct location and 4) first and recurrent infarctions and

5) the period of patient inclusion in the study analyzed should not be > 5 years. Baseline characteristics of the different study populations were recorded.

Internally controlled studies

This term is used for the analysis of studies reporting changes in mortality in two or more patient cohorts admitted to the same institution at different times. These studies are considered separately because they compare patient cohorts prospectively and the patients are from the same geographic location and are studied by the same institution.

Analysis of data and statistical methods

Mortality rates from studies performed during the same time periods (1960 to 1969, 1970 to 1979, or 1980 to 1987) were analyzed and pooled. When not reported specifically by the authors, in-hospital, 1-month or 5-year mortality rates were derived from the data presented.
For each time period, a weighted average mortality rate was calculated by dividing total number of deaths during one period by the total number of patients studied during the same period. Chi-square analysis was used to calculate significant differences between time periods according to average mortality rates. Results were considered to be significant at the level of $p<0.05$. Correlation between the year in which studies were performed (independent variable) and mortality rates (dependent variable) was assessed and regression lines were constructed (14). Regression lines were based on the size of the different studies; this means that weighing factors of studies consist of the number of patients studied.

RESULTS

Fifty-four studies (1,15-67) reporting on prognosis after acute myocardial infarction and performed between 1960 and 1987 were initially identified. Thirty six studies (15-50), with a total of 36,561 patients reported on in-hospital and 1-month or 5-year mortality, or both (Table 1) and therefore were included in this meta-analysis.

Table 1. Characteristics of 36 analyzed studies

Ref	Year of Pub	First Author	Year of Study	Country	No. of Pts	M/F (%)	Mean Age (yr)	In-Hospital Mortality Rate (%)	1-Month Mortality Rate (%)	5-year Mortality Rate (%)	Population-Institution-Based Studies
15	1969	Woodhouse	1960-1964	Canada	783	64/36		26.2		31.7	Institution
16	1973	Geismar	1963	Denmark	1094			41.0		48.0	Population
17	1968	Norris	1966-1967	New Zealand	757	68/32	64.0	26.0			Institution
18	1976	Weinberg	1967-1968	USA	208	75/25	60.5	22.0		27.5	Institution
19	1977	Kitchin	1966-1969	Great Britain	508			17.3		30.0	Institution
20	1987	Djiane	1970-1974	France	731	76/24	63.5	19.2			Institution
			1984-1986		755	74/26	63.7	12.6			
21	1986	Blanc	1972-1973	France	223	59/41	65.0	20.6			Institution
			1982-1983		243	64/36	66.4	20.6			
22	1982	Goldman	1973-1974	USA	4782			22.0			Population
			1978-1979		4786			23.0			
23	1976	O'Rourke	1967-1969	Australia				26.0			Institution
			1973-1975		620		59.4	14.2			
24	1988	Goldberg	1975	USA	763			22.2			Population
			1978		833			20.3			
			1981		978			17.8			
			1984		689			15.1			
25	1988	Dubois	1977-1980	Belgium	1013	83/17	60.5	11.8			Institution
26	1987	Reznik	1979-1980	Australia	2265	69/31	64.0	21.0			Institution

Continuation Table 1.

Ref	Year of Pub	First Author	Year of Study	Country	No. of Pts	M/F (%)	Mean Age (yr)	In-Hospital Mortality Rate (%)	1-Month Mortality Rate (%)	5-year Mortality Rate (%)	Population-Institution-Based Studies
27	1987	Arita	1975-1979	Japan	122	81/19	60.9	18.0			Institution
			1980-1985		264			14.4			
28	1987	Deckers	1981-1982	Netherlands	529			13.6			Institution
29	1988	Deckers	1985-1987	Netherlands	392	66/34	69.5	14.0			Institution
30	1987	Hiramori	1977-1985	Japan	1060	79/21	62.4	14.9			Institution
31	1987	Shibata	1961-1970	Japan	55	73/27	59.0	32.7			Institution
			1971-1975		167	79/21	61.3	22.8			
			1976-1980		261	74/26	62.4	20.3			
			1981-1985		439	73/27	63.3	19.8			
32	1976	Cannom	1971	USA	188	77/23		14.4			Institution
33	1968	Weinblat	1961-1965	USA	881	100/0	52.1		36.0	19.0	Population
34	1977	Hunt	1969-1970	Australia	300	79/21			27.0		Institution
			1974-1975		300	80/20			12.0		
35	1980	Pohjola	1970-1971	Finland	1224	70/30			40.5	30.1	Population
36	1983	Martin	1970-1971	Australia	1078	75/25			38.0	33.6	Population
37	1987	Gomez-Marin	1970	USA	739	73/27	60.6		21.9		Population
			1980		776	71/29	61.1		14.9		
38	1984	Fukui	1972-1975	Japan	29	76/24	61.4		24.1		Institution
			1976-1977		101	78/22	61.2		26.7		
			1978-1979		148	79/21	62.8		23.0		
			1980-1981		214	75/25	61.6		15.4		

Continuation Table 1.

Ref	Year of Pub	First Author	Year of Study	Country	No. of Pts	M/F (%)	Mean Age (yr)	In-Hospital Mortality Rate (%)	1-Month Mortality Rate (%)	5-year Mortality Rate (%)	Population-Institution-Based Studies
39	1983	Wolfenbuttel	1973-1977	Netherlands	254	18/82	57.0		13.0		Institution
40	1982	Sanz	1975-1979	Spain	300	100/0	50.0		5.3		Institution
41	1987	Fukui	1975-1979	Japan	274				22.6		Institution
			1980-1984		516				14.9		
42	1984	Norris	1977-1982	New Zealand	425	100/0	50.0		6.0		Institution
43	1983	Leeder	1979-1980	Australia	614	77/23			26.0		Population
44	1979	Henning	1969-1973	USA	221	77/23	59.6		21.0		Institution
45	1984	Beaglehole	1974	New Zealand					21.5		Population
			1981		905	76/24			23.1		
46	1981	Elveback	1965-1969	USA	300	67/33			18.0	26.8	Population
			1970-1975		385	63/37			9.3	27.2	
47	1976	Helmers	1968-1969	Sweden	475	66/34	65.0			37.9	Institution
48	1980	Luria	1970-1973	USA	143					33.0	Institution
49	1986	Smyllie	1975	Great Britain	175					32.0	Institution
50	1979	Fabricus-Bjerre	1971-1972	Denmark	276	64/36	66.0			47.0	Institution

F=female; M=male; Pts=patients; Pub=publication; Ref=reference

Baseline characteristics

In Table 1, information is also given on the number of patients, age, gender and geographic location. Baseline characteristics of externally controlled studies are listed in Table 2. The following baseline characteristics were commonly reported: gender distribution, mean age, previous myocardial infarction, previous angina, infarct location and risk factors such as positive family history, smoking, hypertension, diabetes mellitus and hypercholesterolemia.

Short-term prognosis: In-hospital mortality

All studies

Eighteen (15-32) of 36 studies reported on in-hospital mortality. A total of 25,508 patients were included in this analysis. Seven studies were performed from 1960 to 1969 in 3,405 patients, 10 studies from 1970 to 1979 in 16,754 patients and 8 studies from 1980 to 1987 in 5,349 patients. The average overall in-hospital mortality rate during the 1960s was 29% and declined to 21% during the 1970s and to 16% during the 1980s (Fig. 1). When results from all 18 studies were pooled, linear regression analysis showed a significant decline in in-hospital mortality over time ($Y = -0.75x + 78$, $r = -0.72$).

Externally controlled studies

Eleven (15-17,20,21,24-26,28-30) of 18 studies including 13,108 patients reporting on in-hospital mortality met the inclusion criteria, whereas 7 studies (18,19,22,23,27,31,32) failed to meet the criteria. The average in-hospital mortality rate calculated for the 1960s, 1970s and 1980s showed a decrease from 32% to 19% to 15%, respectively (Fig. 1). Linear regression analysis of the results from these studies also showed a significant reduction in in-hospital mortality over time ($Y = -0.85x + 85$, $r = -0.82$) (Fig. 2). Only eight studies reported on baseline characteristics of study populations (Table 2a).

Internally controlled studies

Six studies (20,21,23,24,27,31) that included 7,143 patients compared mortality rates between different time periods (Fig. 3). Two studies showed a decline in the in-hospital mortality rate between the 1960s and 1970s. Five studies reported on in-hospital mortality in patient cohorts admitted during the 1970s and 1980s. Three of these studies showed a reduction in in-hospital mortality; the other two showed no differences. Goldman et al. (22) investigated two groups of patients admitted during 1973 to 1974 and 1978 to 1979. The in-hospital mortality rate was 22% and 23%, respectively.

Table 2. Baseline characteristics of externally controlled studies reporting on in-hospital mortality rate

Ref	M/F (%)	Mean Age (yr)	Previous Infarct (%)	Previous Angina (%)	Infarct Ant (%)	Location Post (%)	Positive Family Hx (%)	Smoker (%)	HTN (%)	DM (%)	Hyperchol (%)
A) In-hospital mortality											
1968-1969											
15	64/36										
16											
17	68/32	64.0	29.0	25.0	32.2				19.0	10.0	
1970-1979											
20	76/24	63.5	14.0	29.6			21.6	55.4	29.8	16.7	29.4
21	59/41	65.0	16.0	41.0	34.6	51.1	32.0	33.0	44.0	6.5	45.0
24			34.0								
25	83/17	60.5	27.7	62.5	39.4			84.7	33.3	10.3	
26	69/31	64.0	28.0	46.0			32.0	36.0	38.0	9.0	
1980-1987											
20	74/26	63.7	15.0	17.2			19.2	57.8	31.0	15.0	27.8
21	64/36	66.4	19.0	38.0	34.1	40.8	31.5	33.0	44.0	6.0	32.0
24			36.0								
28											
29	66/34	69.5									
30	79/21	62.4	28.4		54.2	40.4					

Continuation Table 2.

Ref	M/F (%)	Mean Age (yr)	Previous Infarct (%)	Previous Angina (%)	Infarct Ant (%)	Location Post (%)	Positive Family Hx (%)	Smoker (%)	HTN (%)	DM (%)	Hyperchol (%)
B) 1-month mortality											
1970-1979											
36	73/27	60.6									
37	76/24	61.4	17.2		41.7	54.2					
	78/22	61.2	17.8		56.6	36.1					
	79/21	62.8	29.7		50.0	42.3					
43	77/23	59.6	26.0		51.0						
1980-1987											
36	71/29	61.1			52.6	42.2					
37	75/25	61.6	28.0								
44	76/24										

Ant=anterior; DM=diabetes mellitus; F=female; HTN=hypertension; Hx=history; Hyperchol=hypercholesterolemia; M=male; Post=posterior; Ref=reference.

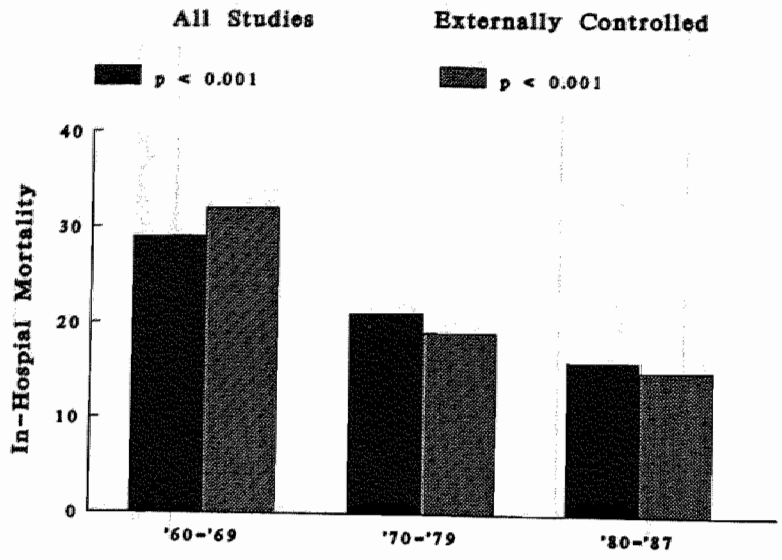

Figure 1. Decline in in-hospital mortality rates as derived from all studies and from externally controlled studies.

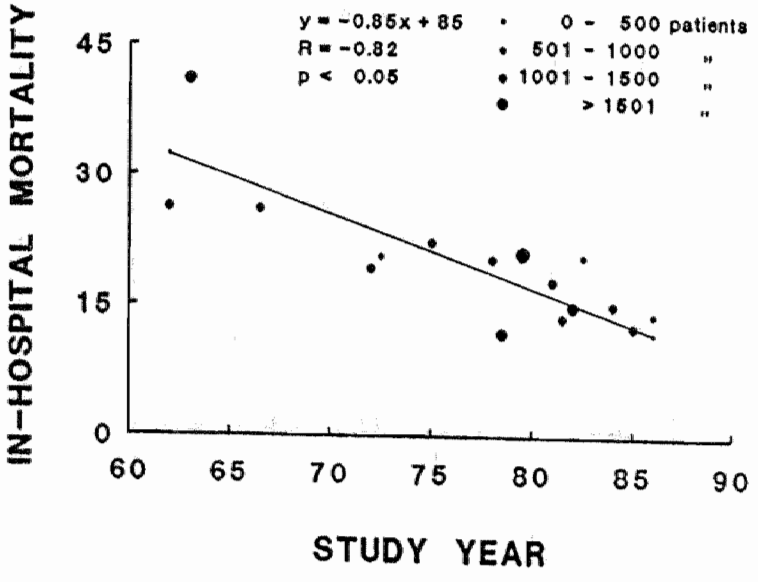

Figure 2. Linear regression analysis of in-hospital mortality rates as derived from externally controlled studies.

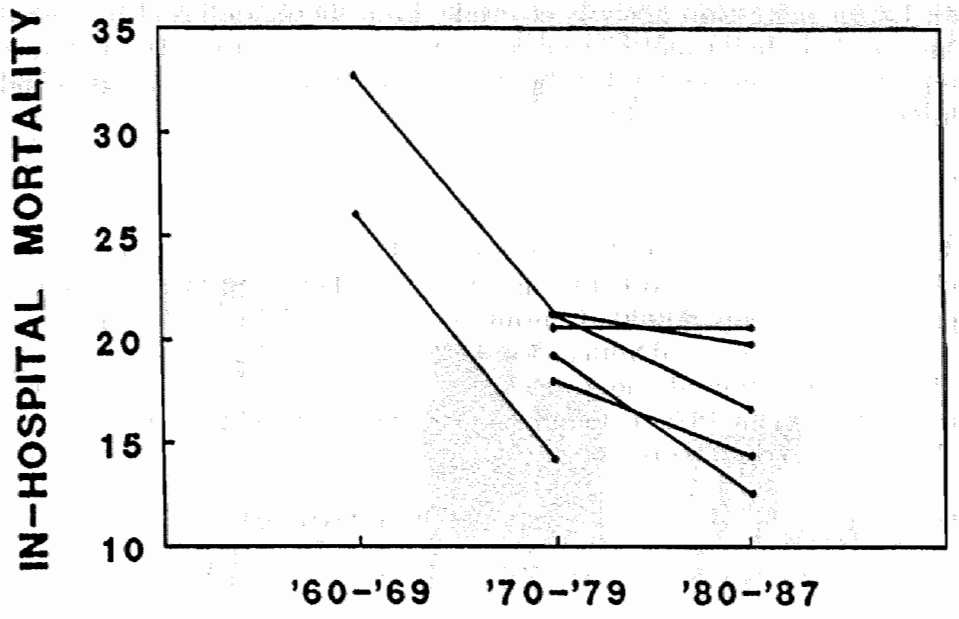

Figure 3. Decline in in-hospital mortality rates as derived from internally controlled studies.

One-month mortality

All studies

The 1-month mortality was documented in 14 studies (33-46) that included 9,984 patients. In two studies with a total of 1,481 patients performed during the 1960s, the average 1-month mortality rate was 31%. Eleven studies with a total of 6,092 patients were performed during the 1970s, resulting in an average 1-month mortality rate of 25%. During the 1980s, the average 1-month mortality rate was 18% as derived from four studies containing 2,411 patients (Fig. 4). In this analysis, a significant decline in overall mortality was also observed ($Y = -1.1x + 109$, $r = -0.59$).

Externally controlled studies

Four (37,38,44,45) of 14 studies that reported on 1-month mortality used identical inclusion criteria. Results of these studies were pooled. During the 1960s no studies that met the inclusion criteria of this analysis were performed. During the 1970s, three studies including 1,238 patients were analyzed. The average 1-month mortality rate was 22% compared with 19% during the 1980s as derived from three studies in a total of 1,895 patients (Fig.

4). Linear regression analysis of results from these studies also showed significant declining mortality rates ($Y = -0.35x + 47$, $r = -0.41$). These studies reported only on gender distribution, mean age, previous infarction and infarct locations (Table 2b).

Internally controlled studies

Six studies (34,37,38,41,45,46) that included 4,987 patients reported on serial changes in 1-month mortality (Fig. 5). Two studies (34,46) concerned two groups of patients admitted during the 1960s and 1970s. The 1-month mortality rate decreased from 27% to 12 % and from 18% to 9%, respectively. Three studies showed about the same reduction (7% to 9%) in 1-month mortality from the 1970s to the 1980s. One study (45) reported no significant change in 1-month mortality.

Long-term prognosis: 5-year mortality after discharge

All studies

Twelve reports containing 13 long-term follow-up studies (15, 16, 18, 19, 33, 35, 36, 46-50) investigated the 5-year mortality rate in hospital survivors. Seven long-term follow-up studies containing 3,091 patients were performed during the 1960s. The average 5-year mortality rate after discharge was 33%. During the 1970s six studies with a total of 2,340 patients were carried out; the average 5-year mortality rate was 33%. Currently, no 5-year follow-up studies are available from the 1980s. Regression analysis showed no decline in 5-year mortality after discharge ($Y = -0.05x + 36$, $r = -0.02$).

Externally and internally controlled studies

No study could be included in the "externally controlled" analysis because each used different inclusion criteria according to the patients studied. Among all studies analyzed, there is one internally controlled study (46) reporting on changes in 5-year mortality after acute myocardial infarction. There was no significant difference between the 5-year mortality rate in survivors admitted during 1965 to 1969 (26.8%) and 1970 to 1975 (27.2%).

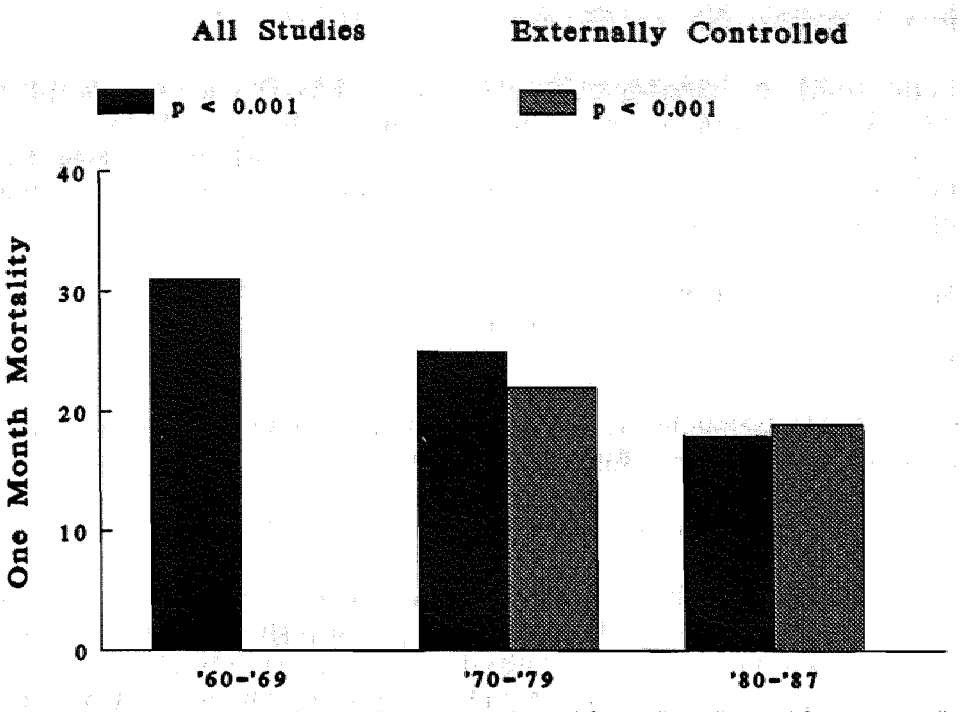

Figure 4. Decline in 1-month mortality rates as derived from all studies and from externally controlled studies.

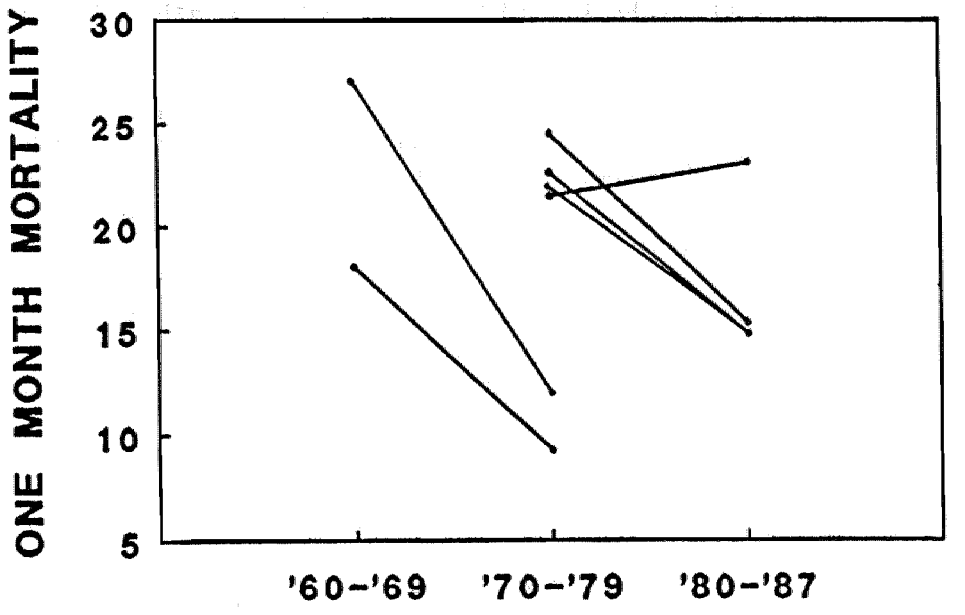

Figure 5. Decline of 1-month mortality rates as derived from internally controlled studies.

DISCUSSION

In this study, we investigated changes in prognosis after acute myocardial infarction by performing a meta-analysis of previously reported studies. This analysis shows an improvement in short-term prognosis after myocardial infarction since 1960. Changes in long-term prognosis after hospital discharge could not be demonstrated.

Short-term prognosis

All studies

A significant decline in overall in-hospital and overall 1-month mortality over the past 3 decades could be shown.

Externally controlled studies

Because overall results may be biased by differences among studies, a subanalysis was performed. This subanalysis also showed an improving trend in short-term prognosis. It was decided that results from studies that met six criteria as listed in the Method section were similar enough to be pooled. Other characteristics of the studies, such as institution and country in which the studies have been performed, were not taken into account. It is possible, however, that these characteristics are a source of bias because of inconsistent trends among different countries in coronary heart disease mortality. However, most countries, including the United States, Australia, New Zealand, Canada, France, Japan, Switzerland and Italy (52) experienced favorable declines in these death rates since the late 1960s; Kimm et al. (68) also reports Belgium and Israel. Among the studies analyzed, only Sweden and Denmark experienced an increase in coronary heart disease mortality during the 1960s until the late 1970s (52,68).

Internally controlled studies

In these studies, a significant reduction in in-hospital and 1- month mortality was also shown. O'Rourke et al. (23) reported a decline in in-hospital mortality from 26% during the 1960s to 14% during the 1970s. This latter figure differs markedly from other mortality rates reported during the 1970s. According to O'Rourke et al. (23), this improvement is due to the introduction of the coronary care unit in 1971. Another factor may have been that most patients admitted to the coronary care unit were < 70 years of age. Because the authors did not report on characteristics of the group of patients admitted during the 1960s, it is difficult to assess whether these two groups are comparable according to baseline variables.

All (20-24) except two (27,31) internally controlled studies that reported on in-hospital mortality had comparable inclusion criteria for their groups studied. Baseline characteristics were not mentioned by all internally controlled studies. Djiane et al. (20) reported only that baseline characteristics such as mean age, gender, risk factors, infarct location and previous infarction were comparable for both groups studied. The baseline characteristics of mean age, risk factors, previous infarction and previous angina were comparable in two groups studied by Blanc et al. (21). However, group 2 contained more men and infarct location were differed significantly in the two groups. Goldman et al. (22) reported only a higher mean age of the patients studied during 1978 to 1979 compared with that of the patients studied during 1973 to 1974. O'Rourke et al. (23) and Goldberg et al. (24) mentioned only that the improvement in in-hospital mortality was not dependent on selection of patients (23) or baseline variables (24).

One-month mortality

Five of six studies (34,37,38,41,45,46) reported on serial reduction in 1-month mortality. Four trials (34,37,38,45) used the same inclusion criteria for the groups studied. Gomez Marin et al. (37) observed no differences in gender and age distribution between the groups studied. Four studies (38,41,45,46) did not specifically report on baseline characteristics. Hunt et al. (34) and Elveback et al.(46) studied groups of patients admitted during, respectively, the 1960s and 1970s. One-month mortality decreased from 27% during the 1960s to 12 % during the 1970s as reported by Hunt et al. (34). This mortality rate of 12% is low according to mortality rates in other reports (37,38,44,45). However, Hunt et al. (34) mentioned that patients in both groups were remarkably similar. Although the age and gender distributions were similar, there were fewer patients with cardiogenic shock and arrest before admission and more with mild infarction in group 2 than in group 1. Group 1 contained more patients with a history of myocardial infarction, angina and smoking and fewer patients with hypertension and diabetes. Elveback et al. (46) reported a decline in mortality from 18% in the 1960s to 9.3% in the 1970s. These low mortality rates may be explained by the fact that only patients without a previous cardiac history were included.

Causes of improvement in in-hospital mortality

Improved mortality may be due to changes in mean hospital stay during the past 30 years. Therefore, we separately analyzed studies reporting on 1-month mortality and found that a reduction in such mortality could be demonstrated as well. A confounding factor in this regard may be differences in baseline characteristics among the patient studied. The admission of patients with less severe disease may have lowered the in-hospital mortality

rate (24). However, this factor may have been counteracted by a trend, reported in some internally controlled studies (31,38), toward earlier hospital admission during the past 3 decades, which may have resulted in admission of patients with more severe disease.

There is no wide range in results of studies performed during one decade. It is unlikely that patients admitted in 1979 were very dissimilar from those admitted in 1981. We therefore conclude that differences in mortality rates between different time periods are caused by improved medical care during the 1970s and 1980s. Since 1968, mortality from coronary heart disease has decreased in the United States and many other parts of the world (1,52,69,70). The cause for this decline is complex and includes changes in diet and in life-style, as well as the introduction of new methods in the diagnosis and treatment of coronary heart disease. Acute myocardial infarction accounts for about 33% of coronary heart disease mortality, so it seems likely that improvement in short-term prognosis after acute myocardial infarction has contributed to reduction in overall cardiac mortality.

Long-term prognosis

In contrast to short-term prognosis, no change in overall 5-year mortality after hospital discharge could be shown. Subgroups of studies using identical inclusion criteria could not be constructed. Weinblatt et al. (33) included only men with a first acute myocardial infarction. These men had a mean age of 52 years and a 5-year mortality rate of only 19%.

Essential baseline information such as age and gender distribution, risk factors and previous history were often incompletely recorded or missing. However, all but one (37) long-term internally controlled study showed no improvement in long-term prognosis over time. Gomez Marin et al. (37) showed an improvement in 4-year mortality between 1970 and 1980. Elveback et al. (46) and Weinblatt et al. (51) studied long-term survival in two groups of patients who survived their first myocardial infarction during, respectively, the 1960s and 1970s. No difference in survival between those two periods was found. Goldberg et al. (24,52) reported improved short-term but not long-term survival after acute myocardial infarction in Worcester, Massachusetts from 1975 through 1984.

Reasons for lack of improvement in long-term prognosis

This lack of improved long-term prognosis reported by internally controlled studies could not be explained by differences among groups according to inclusion criteria or baseline characteristics (24,51,52). It may be explained by the progression of underlying coronary artery disease or failure to influence variables which affect survival after hospital discharge (24). Almost

all studies that were analyzed reported on patients before the introduction of thrombolytic therapy and coronary angioplasty after myocardial infarction.
A recent study by Simoons et al. (71) showed that in a selected group of patients with acute myocardial infarction, administration of thrombolytic therapy improved 5-year survival. The long-term value of these interventions needs to be documented in less selected groups of patients.

Limitations of this study

Publication bias may be a confounding factor in meta-analysis, because studies that report less favorable results are often not published and therefore not included. It is unlikely that publication bias may explain the decline in short-term mortality over time. It is, however, likely that a study reporting a 25% in-hospital mortality rate would not be submitted for publication at present, whereas this apparently was not a problem in the 1960s when these figures were not unusual.
Meta-analysis has been criticized for comparing and aggregating studies that include very different methods, treatments and populations (13). We tried to solve this problem by performing two subanalyses.
To facilitate comparison of studies on prognosis after myocardial infarction in the future, investigators should use more comparable inclusion criteria. They also must report more extensively on baseline characteristics than has been done in the past.

REFERENCES

1. Aberg A, Bergstrand R, Johansson S, et al. Declining trend in mortality after myocardial infarction. Br Heart J 1984;51:346-51.
2. Lown B, Fakhro AM, Hood WB Jr, Thorn GW. The coronary care unit: new perspectives and directions. JAMA 1967;199:188-98.
3. Sones FM, Shirey EK. Cine coronary arteriography. Mod Concepts Cardiovasc Dis 1962;31:735-42.
4. Effler DB. Myocardial revascularization surgery since 1945: its evolution and impact. J Thorac Cardiovasc Surg 1976;72:8-23.
5. Gruentzig A, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary artery stenosis: Percutanious transluminal coronary angioplasty. N Engl J Med 1979;301:61-8.
6. Forrester JS, Diamond G, Chatterjee K, Swan HJC. Medical therapy of acute myocardial infarction by application of hemodynamic subsets (first of two parts). N Engl J Med 1976;295:1356-62.
7. Clauss RH, Birtwell WC, Albertel GA, et al. Assisted circulation: the arterial counterpulsation. J Thorac Cardiovasc Surg 1961;41:447-54.

8. The Norwegian Multicenter Study Group. Timolol-induced reductions in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304: 801-7.
9. Sixty-Plus Reinfarction Study Group. A double blind trial to assess long-term anticoagulant therapy in elderly patients after myocardial infarction. Lancet 1980;2:989-94.
10. Didisheim P, Foster V. Actions and clinical status of platelet suppressive agents. Semin Hematol 1978;15:55-72.
11. Rentrop P, De Vivie ER, Karsch DR, et al. Acute myocardial infarction: intracoronary application of nitroglycerin and streptokinase in combination with transluminal recanalization. Clin Cardiol 1979;5:354-63.
12. Simoons ML, Serruys PW, Van den Brand M, et al. Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. J Am Coll Cardiol 1986; 717-28.
13. Wolf FM. Meta-Analysis: Quantitative methods for research synthesis. Beverly Hills: Sage University Paper series on Quantitative Applications in the Social Sciences, 07-059,1986:10-7.
14. Weisberg S. Simple linear models. In: Weisberg S. Applied Linear Regression. New York: Wiley, 1980:1-30.
15. Woodhouse SP. Subsequent mortality in patients surviving myocardial infarction. N Z Med J 1969;69:24-7.
16. Geismar P, Iversen E, Mosbech J, Deyer K. Long-term survival after myocardial infarction: a national follow-up study on 642 patients in Denmark. Int J Epidemiol 1973;2:257-63.
17. Norris RM, Bensley KE, Caughey DE, Scott PJ. Hospital mortality in acute myocardial infarction. Br Med J 1968;3:143-6.
18. Weinberg SL. Natural history six years after acute myocardial infarction: is there a low-risk group? Chest 1976;69:23-8.
19. Kitchin AH, Pocock SJ. Prognosis of patients with acute myocardial infarction admitted to a coronary care unit.II. Survival after hospital discharge. Br Heart J 1977;39:1167-71.
20. Djiane P, Bory M, Villain P, et al. Le pronostic de l'infarctus du myocarde recent a-t-il change? Arch Mal Coeur 1987;13:1883-92.
21. Blanc JJ, Ropars G, Boschat J, Etienne Y, Penther P. Comparaison de deux groupes de patients hospitalises a 10 ans d 'intervalle pour un infarctus du myocarde recent. Arch Mal Coeur 1986;79:143-51.
22. Goldman L, Cook F, Hashimoto B, Stone P, Muller J, Loscalzo A. Evidence that hospital care for acute myocardial infarction has not contributed to the decline in coronary mortality between 1973-1974 and 1978-1979. Circulation 1982;65:936-42.
23. O'Rourke MF, Walsh B, Fletcher M, Crowley A. Impact of the new generation coronary care unit. Br Med J 1976;2:837-9.
24. Goldberg RJ, Gore JM, Alpert JS, Dalen JE. Incidence and case fatality rates of acute myocardial infarction (1975 - 1984): the Worcester Heart Attack Study. Am Heart J 1988;115:761-7.
25. Dubois C, Pierard LA, Albert A, et al. Short-term risk stratification at admission based on simple clinical data in acute myocardial infarction. Am J Cardiol 1988;61:216-9.
26. Reznik R, Ring I, Fletcher P, Berry G. Mortality from myocardial infarction in different types of hospitals. Br Med J 1987;294:1121-5.
27. Arita M, Ueno Y, Mohara O, et al. The cause of death, risk factors and long-term prognosis of acute myocardial infarction. Jpn Circ J 1987;51:332-7.

28. Deckers JW, Fioretti P, Brower RW, Baardman T, Beelen A, Simoons ML. Prediction of 1-year outcome after complicated and uncomplicated myocardial infarction: Bayesian analysis of predischarge exercise test results in 300 patients. Am Heart J 1987;113;90-5.
29. Deckers JW, Veerhoek MJ, Smits R, Leenders CM. Sterfte op hartbewakingsafdeling van klein algemeen ziekenhuis. Hart Bull 1988;19:179-82.
30. Hiramori K. Major causes of death from acute myocardial infarction in a coronary care unit. Jpn Circ J 1987;51:1041-7.
31. Shibata J, Tanazawa S, Hirasawa K, Tateda K, Kanda M. Deaths in early phase of acute myocardial infarction and approaches for reducing the in-hospital and out-hospital case-fatality rates of the disease. Jpn Circ J 1987;51:325-31.
32. Cannom DS, Levy W, Cohen LS. The short- and long-term prognosis of patients with transmural and nontransmural myocardial infarction. Am J Med 1976;61:452-8.
33. Weinblatt E, Shapiro S, Frank CW, Sager RV. Prognosis of men after first myocardial infarction: mortality and first recurrence in relation to selected parameters. Am J Public Health 1968;58:1329-47.
34. Hunt D, Sloman G, Christie D, Penington C. Changing patterns and mortality of acute myocardial infarction in a coronary care unit. Br Med J 1977;1:795-8.
35. Pohjola S, Siltanen P, Romo M. Five-year survival of 728 patients after myocardial infarction: a community study. Br Heart J 1980;43:176-83.
36. Martin CA, Thompson PL, Armstrong BK, Hobbs MST, De Klerk N. Long-term prognosis after recovery from myocardial infarction: a nine year follow-up of the Perth Coronary Register. Circulation 1983;68:961-9.
37. Gomez-Marin O, Folsom AR, Kottke TE, et al. Improvement in long-term survival among patients hospitalized with acute myocardial infarction, 1970 to 1980. N Engl J Med 1987;316:1353-9.
38. Fukui S, Satoh K, Ueki N, et al. Immediate prognosis in acute myocardial infarction: serial changes in immediate mortality rate and cause of death. Jpn Circ J 1984;48:11-7.
39. Wolfenbuttel BHR, Verdouw PD, Scheffer MG, Bom HPA, Bijleveld RE, Hugenholtz PG. Significance of haemodynamic variables in coronary care unit for prediction of survival after acute myocardial infarction. Br Heart J 1983;50:266 -72.
40. Sanz G, Castaner A, Betriu A, et al. Determinants of prognosis in survivors of myocardial infarction: a prospective clinical angiographic study. N Engl J Med 1982;306:1065-70.
41. Fukui S, Tani A, Hamano Y, Katoh O, Suzuki K, Minamino T. Immediate and long-term prognosis of acute myocardial infarction: analysis of determinants of prognosis. Jpn Circ J 1987;51:344-51.
42. Norris RM, Barnaby PF, Brandt PWT, et al. Prognosis after recovery from first acute myocardial infarction: Determinants of reinfarction and sudden death. Am J Cardiol 1984;53:408-13.
43. Leeder SR, Dobson AJ, Gibberd RW, Flynn SJ. Attack and case fatality rates for acute myocardial infarction in the hunter region of New South Wales, Australia, in 1979. Am J Epidemiol 1983;118:42-51.
44. Henning H, Gilpin EA, Covel JW, Swan EA, O'Rourke RA, Ross J. Prognosis after acute myocardial infarction: a multi-variate analysis of mortality and survival. Circulation 1979;59:1124-34.
45. Beaglehole R, Bonita R, Jackson R, Stewart A, Sharpe N, Fraser GE. Trends in coronary heart disease event rates in New Zealand. Am J Epidemiol 1984;120:225-35.

46. Elveback LR, Connolly DC, Kurland LT. Coronary heart disease in residents of Rochester, Minnesota. II. Mortality, incidence, and survivorship, 1950 - 1975. Mayo Clin Proc 1981;56:665-72.
47. Helmers C, Lundman T, Maasing R, Wester PO. Mortality pattern among initial survivors of acute myocardial infarction using a life-table technique. Acta Med Scand 1976;200:469-73.
48. Luria MH. Long-term survival after recovery from acute myocardial infarction. Compr Ther 1980;6:36-41.
49. Smyllie HC. Prognosis of patients discharged from a coronary care unit. Br Med J 1986;293:541-2.
50. Fabricius-Bjerre N, Munkvad M, Bjerre Knudsen J. Subendocardial and transmural myocardial infarction: a five year survival study. Am J Med 1979;66:986-90.
51. Weinblatt E, Goldberg JD, Ruberman W, Frank CW, Monk MA, Chaudhary BS. Mortality after first myocardial infarction: search for a secular trend. JAMA 1982;247:1576-81.
52. Goldberg RJ, Gore JM, Alpert JS, Dalen JE. Recent changes in attack and survival rates of acute myocardial infarction (1975 through 1981). JAMA 1986;255:2774-9.
53. Cooperative Study. Death rate among 795 patients in first year after myocardial infarction. JAMA 1966;197:184-6.
54. Krone RJ, Friedman E, Thanavaro S, Miller JP, Kleiger RE, Oliver GC. Long-term prognosis after first Q-wave (transmural) or non-Q-wave (nontransmural) myocardial infarction: analysis of 593 patients. Am J Cardiol 1983;52:234-9.
55. Norris RM, Caughey DE, Mercer CJ, Scott PJ. Prognosis after myocardial infarction: six-year follow-up. Br Heart J 1974;36:786-90.
56. Cleempoel H, Vainsel H, Dramaix M, et al. Limitations on the prognostic value of predischarge data after myocardial infarction. Br Heart J 1988;60:98-103.
57. Norris RM, Caughey DE, Deeming LW, Mercer CJ, Scott PJ. Coronary prognostic index for predicting survival after recovery from acute myocardial infarction. Lancet 1970;2:485-7.
58. Kentala E, Pyorala K, Heikkila J, Sarna S, Luurila O. Factors related to long-term prognosis following acute myocardial infarction. Scand J Rehab Med 1975;7:118-24.
59. Schroeder JS, Lamb IH, Hu M. Do patients in whom myocardial infarction has been ruled out have a better prognosis after hospitalization than those surviving infarction? N Engl J Med 1980;303:1-5.
60. Moss AJ, DeCamilla J, Engstrom F, Hoffman W, Odoroff C, Davis H. The posthospital phase of myocardial infarction: identification of patients with increased mortality risk. Circulation 1974;49:460-6.
61. Murray DP, Salih M, Lip Bun Tan, Murray RG., Littler WA. Prognostic stratification of patients after myocardial infarction. Br Heart J 1987;57:313-8.
62. Vedin A, Wilhelmsson C, Elmfeldt D, Save-Soderbergh J, Tibblin G, Wilhelmsen L. Deaths and non-fatal reinfarctions during two years follow-up after myocardial infarction. Acta Med Scand 1975;198:353-64.
63. Norris RM, Caughey DE, Deeming LW, Mercer CJ, Scott PJ. Prognosis following acute myocardial infarction. N Z Med J 1973;77:12-8.
64. Madigan NP, Rutherford BD, Frye RL. The clinical course, early prognosis and coronary anatomy of subendocardial infarction. Am J Med 1976;6:634-41.
65. Marcus FI, Cobb LA, Edwards JE, et al. Mechanism of death and prevalence of myocardial ischemic symptoms in the terminal event after acute myocardial infarction. Am J Cardiol 1988; 61:8-15.

66. Moss AJ, Decamilla J, Davis H, Bayer L. The early posthospital phase of myocardial infarction. Circulation 1976;54:58-64.
67. Moss AJ, Decamilla J, Davis H. Cardiac death in the first 6 months after myocardial infarction: potential for mortality reduction in the early posthospital period. Am J Cardiol 1977;39:816-20.
68. Kimm SY, Ornstein SM, DeLong ER, et al. Secular trends in ischemic heart disease mortality: regional variation. Circulation 1983;1:3-8.
69. Levy RI. Causes of the decrease in cardiovascular mortality. Am J Cardiol 1984;54:7C-13C.
70. Feinleib M. The magnitude and nature of the decrease in coronary heart disease mortality rate. Am J Cardiol 1984;54:2C-6C.
71. Simoons ML, Vos J, Tijssen JGP, et al. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. J Am Coll Cardiol 1989;14:1609-15.

CHAPTER 3

Changing Characteristics and In-Hospital Outcome of Patients Admitted With Acute Myocardial Infarction

Observations from 1982 to 1994

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ABSTRACT

During the past decade various new treatments became available for patients with acute myocardial infarction. The effects of these treatment modalities have been studied extensively in selected patient groups. These studies indicate that early diagnosis, risk stratification and prompt initiation of treatment are of crucial importance for optimal benefit. However, it is not known whether prognosis changed in all patients admitted with an acute myocardial infarction. Also the characteristics of the infarct population may have changed over time because of new medication regimens, invasive interventions and awareness of the importance of risk factors.

We studied all patients admitted with acute myocardial infarction in 1982, 1988 and 1994. Information on baseline characteristics, clinical variables and all interventions was collected.

In those 3 years 223, 227 and 235 patients were admitted because of an acute myocardial infarction. Patients admitted in 1994 were older, more often female and less often had a previous cardiac history. More patients admitted in that year had previous balloon angioplasty and coronary bypass grafting. Smoking habits decreased during the past decade. In-hospital mortality was 38 (17%) in 1982, 23 (10%) in 1988 and 22 (9%) in 1994 ($p<0.05$). Variables related to high risk for in-hospital death in 1982 were higher age, low systolic blood pressure, atrial fibrillation, absence of accelerated idioventricular rhythm, sustained ventricular tachycardia and signs of left ventricular dysfunction; in 1988 the occurrence of non-sustained ventricular tachycardia, Killip class more than I, the absence of thrombolytic therapy, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) were independently related to in-hospital death. In 1994 high risk variables for in-hospital death were dyspnea on admission, sustained ventricular tachycardia, female gender, higher creatinine on admission, and a previous cardiac history.

Conclusion: In-hospital mortality for unselected patients admitted with an acute myocardial infarction decreased between 1982 and 1988 and remained the same between 1988 and 1994, in spite of further ageing of the population. In the study period there has been a change in baseline characteristics and high risk variables for in-hospital death after myocardial infarction.

INTRODUCTION

The reported decline in mortality from coronary heart disease has been explained by a decreased incidence and prevalence because of changes in life style (diet, smoking, exercise) resulting in a decrease in risk factors, better pharmacological control of hypertension and new modes of treatment in the acute and chronic stage of ischemic heart disease. (1-7). The in-hospital outcome of patients admitted with acute myocardial infarction has been the subject of many studies during the past 30 years. A meta-analysis from our group and data from other studies showed that the hospital outcome improved during the 1960's, 1970's and 1980's (8,9). This decline in mortality has been related to different factors in each decennium (10). In the 1960's (hospital mortality 22-29%) the widespread use of coronary care units and the development of defibrillators reduced early mortality by about 5% (11). In the 1970's (hospital mortality 17-21%) the use of the Swan-Ganz catheter and the introduction of different pharmacological treatments reduced mortality by approximately 4%. During the 1980's in-hospital mortality rates decreased further to 13-16% related to the introduction of thrombolytic therapy and the widespread use of antiplatelets and anticoagulant drugs, beta-blockers and the advent of coronary angioplasty (8,9,12-14).
Treatment of patients admitted with acute myocardial infarction has changed considerably during the 1980's. Until the end of the 1970's treatment of acute myocardial infarction consisted of pain relief and management of complications such as arrhythmias, heart failure and persisting ischemia. In the late 1980's and early 1990's treatment focussed on early reperfusion of the infarct related artery, after the use of thrombolytic agents showed improvement in left ventricular function and reduction of mortality (12,15-19). Also balloon angioplasty, coronary bypass grafting and a variety of new drugs were introduced in the acute and chronic phase of coronary heart disease. The purpose of this study has been to investigate a change in patient characteristics and hospital outcome in unselected patients admitted with an acute myocardial infarction.

METHODS

The study was performed at the department of cardiology of the Academic Hospital of Maastricht, the Netherlands. This is the only hospital in an area with approximately 182,000 inhabitants and therefore serves in this area as a primary hospital for acute ischemic heart disease. All patients from the area with signs of acute ischemic heart disease are brought to this hospital. Only rarely are patients from the area admitted to other hospitals. The hospital records of all patients originating from the Maastricht area, admitted in 1982, 1988 or 1994 with myocardial infarction, unstable angina pectoris or possible

acute ischemia were reviewed. As a rule, the patients were admitted on the coronary care unit and only exceptionally to the general cardiology department of our hospital or to another hospital in the region. The admission diagnosis of acute myocardial infarction was made if there was a history of typical chest pain of more than 30 min duration, accompanied by ST-segment elevation of more than 0.1 mV in at least one extremity lead or precordial lead. Right ventricular involvement in patients with an inferior infarction was diagnosed when ST-segment elevation was present equal to or more than 0.1 mV, with a positive T wave in the right precordial lead V4. In patients with a recurrent myocardial infarction the same criteria were required. Patients showing ST-segment depression indicative for posterior infarction were also included. Extension of an old infarction prior to admission was diagnosed when new typical chest pain occurred combined with increased ST-segment elevation or depression compared to the most recent ECG after the previous infarction and a typical enzyme rise. Patients presenting with either left or right bundle branch block were also included if the history was suggestive of myocardial infarction and the diagnosis confirmed by typical plasma enzyme changes. No secondary or tertiary referral patients were included. Age or previous medical history were no reason for exclusion. A final diagnosis of myocardial infarction was made if there was a typical rise of creatine kinase, aspartate aminotransferase and lactic dehydrogenase above the upper limit of normal (40 U/l).
Clinical variables were collected with emphasis on medical and invasive treatment. The use of various medications was registered on admission and during hospital stay. All interventions such as thrombolytic therapy, percutaneous transluminal coronary angioplasty and coronary artery bypass grafting were registered. To evaluate the role of thrombolytic therapy, we introduced a variable in the patient groups; 'eligible for thrombolytic therapy'. For all three time periods the same criteria for this variable were used: chest pain of less than 6 hours in duration, ST-segment elevation of more than 0.1 mV in at least two inferior leads or three anterior leads and no contraindications for thrombolytic therapy.

Statistical analysis

The data were analysed by using the Statistical Package of the Social Sciences (20) and the SAS program (21). Bivariate analysis was performed with Student t-test to compare groups with continuous variables and Chi-square for groups with discrete variables. To correct for cells with an expected count less than 5, the likelihood ratio chi- square was used and Fisher's exact test. Variables reaching significance in the bivariate analysis together with other relevant variables, were used in a multiple regression analysis. For these variables also sensitivity, specificity and positive predictive accuracy were also calculated. The independent importance of different variables was

calculated for in-hospital death. Data are presented as mean ± standard deviation.

Changes in treatment between the study years

Treatment in 1982 consisted of admission to the coronary care unit, continuous arrhythmia monitoring, intravenous pain relief with morphinomimetics, prophylaxis of ventricular fibrillation by lidocaine unless contraindicated and when indicated hemodynamic monitoring using a Swan-Ganz catheter. Cardiac failure was treated with i.v. diuretics and sympathicomimetic drugs if needed. Beta-blockers, calcium antagonists, coumarin derivates, oral nitrates and antiplatelet drugs were not prescribed routinely but only given for specific indications (table 2). Thrombolytic therapy, PTCA and CABG were applied in a very small number of patients.
In 1988 and 1994 patients with acute myocardial infarction (MI) were admitted to the coronary care unit and treated with intravenous heparin and nitroglycerin if not contraindicated. Thrombolytic therapy was started when no contraindications were present and the duration of chest pain was less than 6 hours. Primary PTCA was performed in patients with a contraindication for thrombolytic therapy, patients with a changing pattern of ST-segment elevation and severity of chest pain and also in the case of impaired hemodynamics.
Coronary arteriography (CAG) followed by rescue PTCA was performed when no reperfusion occurred as assessed by non-invasive signs of reperfusion: disappearance of chest pain, ST-segment normalization or occurrence of reperfusion arrhythmias. CAG could also be performed in the setting of study protocols. Late CAG was performed in case of ischemia in rest or during exercise testing. PTCA or CABG were performed in case of residual ischemia and in patients with marked abnormalities at CAG, as judged by the attending clinician. Medical treatment at discharge consisted mostly of beta-blockers, aspirin and nitrates.
In 1994, patients with anterior myocardial infarction resulting in a diminished left ventricular function were treated with ACE-inhibitors resulting in 24% of patients discharged on these drugs. Most patients were included in study protocols evaluating the safety and efficacy of new thrombolytic agents. In the absence of non-invasive signs of reperfusion, the majority of infarction patients were referred for acute coronary angiography and if indicated followed by balloon angioplasty or coronary bypass grafting. In the case of severe multivessel disease an intra-aortic balloon pump was inserted frequently as a bridge to CABG. Also in patients with a large infarction after reperfusion therapy an aortic balloon pump was inserted.

Table 1. Baseline characteristics and interventions of patients with myocardial infarction in 1982, 1988, 1994.

	1982		1988		1994	
N	223		227		235	
age (mean ± SD)*	64.8 ± 11.1		63.9 ± 12.1		66.2 ± 11.2	
male *	151	(68)	166	(73)	146	(62)
smoking *	135	(61)	108	(48)	114	(48)
diabetes	33	(15)	27	(12)	21	(9)
hypertension	89	(40)	75	(33)	84	(36)
previous infarction	62	(28)	52	(23)	49	(21)
previous PTCA *	0		2	(1)	11	(5)
previous CABG *	3	(1)	12	(5)	13	(6)
75% admitted within *	6 hours		3.5 hours		2.5 hours	
thrombolytics *	3	(1)	62	(27)	68	(29)
thrombolytics + rescue PTCA *	0		27	(12)	25	(11)
primary PTCA *	0		10	(4)	26	(11)
late thrombolytics *	0		10	(4)	6	(3)
late PTCA *	1	(.4)	18	(8)	59	(25)
CABG *	0		11	(5)	18	(8)

* p is at least <.05, CABG=coronary artery bypass grafting, PTCA=balloon angioplasty, SD=standard deviation, Percentages between brackets.

RESULTS

Baseline characteristics

Table 1 shows demographic characteristics of all patients. The number of patients remained the same in the three study years; in 1982, 223; in 1988, 227 and in 1994, 235 patients were admitted with an acute myocardial infarction. However the mean age increased and patients admitted in 1994 were significantly older. In 1982, 125 had inferior MI (33 with right ventricular involvement) and 98 had anterior MI. In 1988 there were 146 with inferior MI (49 right ventricular involvement) and 81 with anterior MI. Finally in 1994, 148 had inferior MI (50 with right ventricular involvement) and 87 had anterior MI (Table 5). Table 1 also shows that differences were found for delay time between onset of symptoms and the admission time, smoking, and gender. Seventy five percent were admitted within 2.5 hours in 1994 whereas this required 3.5 hours in 1988 and 6 hours in 1982 ($p<0.05$). Smoking was less frequent in 1988 and 1994 (48% vs 61% in 1982; $p<0.01$). Patients admitted in 1994 had significantly more frequent previous PTCA or CABG as compared to 1982. Heparin and nitroglycerin was the initial treatment in about 70% of the 1988 and 1994 patients.

In 1988 an acute intervention was performed in 43% (27% thrombolytics, 12% thrombolytics followed by rescue PTCA, 4% primary PTCA).
In 1994, 51% underwent an acute intervention (29% thrombolytics, 11% thrombolytics followed by PTCA, 11% acute PTCA) (table 1).
Drug treatment varied significantly between the years as is shown in table 2, reflecting new insights because of the results of clinical trials with various new drugs. Aspirin, beta blockers, calcium antagonists and ACE inhibitors were more often prescribed in the 1988 and 1994 patients whereas the use of nitrates, diuretics, coumarins and digoxin was more frequent in 1982.

In-hospital mortality and morbidity

Table 3 shows baseline characteristics of survivors versus non-survivors. In 1982, 38 (17%) patients died in hospital. None of these patients had received thrombolytic therapy, PTCA or CABG. The number of patients over the age of 70 years was 84 (38%) (of whom 26 (31%) died).
In 1988, 23 (10%) patients died in hospital ($p<0.05$). Of those, 4 patients had received thrombolytic therapy, primary PTCA in 1, rescue PTCA in 1, and CABG in 1. In 1988, 70 (31%) patients were over the age of 70 years of whom 13 (19%) died.
In 1994, 22 (9%) patients died in hospital. Of those 3 received thrombolytic therapy, 1 primary PTCA, 3 rescue PTCA and 2 CABG. In 1994, 89 (39%) were older than the age of 70. Of these patients 15 (17%) died.
The causes of death are listed in table 4. It is shown that the most frequent cause of death was pump failure in all three years. However there was an increase in patients dying from pump failure (40%-48%-66%) and a decrease in the number of arrhythmic deaths (13%-9%-5%). In 1994 less patients died of recurrent infarction.
In 1982, 125 patients had inferior (33 with right ventricular involvement) and 98 anterior myocardial infarction. Mortality was highest in patients with anterior myocardial infarction admitted in 1982, 26% vs. 16% in 1988 and 11% in 1994 ($p<0.01$). Hospital mortality from inferior myocardial infarction with right ventricular involvement decreased from 15% in 1982 to 10% in 1988 and 12% in 1994. The difference between the number of right ventricular infarctions in all years (33 vs 49 and 50) could be explained by the fact that right precordial recordings were not performed routinely in 1982 (Table 5).

Table 2. Drugs before admission, and at discharge in 1982 and 1988 and 1994. Figures are percentages. For all drugs there is a significant difference in the number of prescriptions between the years.

	1982		1988		1994	
	pre-admission	discharge	pre-admission	discharge	pre-admission	discharge
Beta blockers	13	29	30	53	26	58
Nitrates	28	79	27	50	21	73
Aspirin	4	5	11	73	24	72
Calcium ant.	6	28	15	46	17	23
Diuretics	26	59	18	19	18	16
Coumarins	9	37	7	19	4	16
ACE inhibitors	0	0	4	10	9	24
Digoxin	11	46	7	10	4	10

Table 3. Baseline characteristics of survivors and non-survivors.

	Death 1982 n=38	Survivors 1982 n=185	Death 1988 n=23	Survivors 1988 n=204	Death 1994 n=22	Survivors 1994 n=213
mean age	71.8	61.6***	71.5	61.7***	74.6	65.3***
>70 years	26 (68)	58 (31)**	13 (57)	57 (28)*	15 (68)	74 (35)**
male	20 (53)	131 (71)*	13 (57)	153 (75)	6 (27)	140 (66)***
fam. Hist. Pos.	28 (74)	116 (63)	11 (48)	114 (56)	5 (22)	86 (44)
smoking	16 (42)	119 (64)*	8 (35)	105 (51)	5 (22)	108 (51)*
diabetes	8 (21)	25 (14)	2 (9)	15 (7)	3 (14)	18 (8)
hypertension	16 (42)	73 (39)	11 (48)	64 (31)	12 (55)	72 (34)
previous CVA	4 (11)	14 (8)	2 (9)	10 (5)	5 (23)	7 (3)***
previous angina	20 (53)	81 (44)	10 (43)	79 (39)	9 (41)	48 (23)
previous MI	11 (29)	51 (28)	8 (35)	44 (22)	8 (38)	41 (19)
previous PTCA	0	0	0	2 (1)	1 (5)	10 (5)
previous CABG	0	3 (2)	1 (4)	11 (5)	1 (5)	12 (6)

*=p<.05 **=p<.01 ***=p<.001, differences within one year. CABG= coronary bypass grafting, MI = myocardial infarction, CVA = cerebro vascular accident, PTCA = balloon angioplasty, Fam. Hist. Pos = positive family history of coronary heart disease. Percentages within brackets.

Table 4. Causes of death (percentages between brackets)

	1982 n=38*	1988 n=23	1994 n=22
arrhythmic	5 (13)	2 (9)	1 (5)
recurrent infarct	7 (18)	6 (26)	1 (5)
pump-failure	15 (40)	11 (48)	14 (66)
other cardiac	9 (24)	3 (13)	3 (12)
non cardiac	2 (5)	1 (4)	3 (12)

* p<.05 difference in total mortality between 1982 and 1988/1994

Table 5. Location of infarction in relation to mortality in-hospital

	1982			1988			1994		
	N	death	%	N	death	%	N	death	%
Inferior	92	8	9	97	5	5	98	6	6
Inferior +RVI	33	5	15	49	5	10	50	6	12
Anterior	98	25	26	81	13	16	87	10	11
All *	223	38	17	227	23	10	235	22	9

RVI=inferior myocardial infarction with right ventricular infarction. *=p<.05 (difference in total mortality between 1982 and 1988/1994)

Eligibility for thrombolytic therapy

In 1982, 115 patients were eligible for thrombolytic therapy of whom 16 (14%) died, only 3 actually received this kind of treatment and all survived. In 1988, 124 patients were eligible for thrombolytic therapy of whom 9 (7%) died; 89 (39%) received the drug on admission and 10 (4%) later during admission because of recurrent infarction. Of the 99 patients that received thrombolytic therapy, 4 died in-hospital.
In 1994, 119 patients were eligible for thrombolytic therapy of whom 7 (6%) died; 93 (40%) patients received thrombolytics of whom 4 died.

Morbidity

Morbidity was assessed in terms of residual angina pectoris and dyspnea at discharge according to the criteria of the New York Heart Association. In 1988 and 1994 more patients had angina pectoris functional class 1 and/or dyspnea functional class 1 prior to discharge as compared to 1982 (87% - 72%). Due to the worse preadmission functional class of the patients in 1982, more improvement was found in this group than in 1988.

Table 6. Admission variables of prognostic importance for in-hospital death

variable	p.	Sensitivity	Specificity	PPV	P.
1982					
Age >70	<0.001	0.74	0.68	0.33	0.0031
Sustained VT	<0.001	0.21	0.96	0.53	0.0090
Atrial fibrillation	<0.001	0.29	0.92	0.44	0.0026
No AIVR	0.088	0.95	0.16	0.19	0.0605
Systolic BP <100	<0.05	0.32	0.89	0.37	0.0500
Heart failure	<0.001	0.76	0.62	0.29	0.0023
Killip > I	<0.001	0.46	0.66	0.21	0.0514
1988					
NSVT's	<0.05	0.45	0.71	0.14	0.0310
Killip > I	<0.001	0.61	0.87	0.35	0.0001
No intervention	<0.05	0.74	0.84	0.16	0.0285
1994					
No cardiac history	<0.01	0.68	0.64	0.16	0.0113
Dyspnea on admission	<0.001	0.50	0.92	0.38	0.0000
Sustained VT	<0.001	0.18	0.97	0.36	0.0043
creatinine on admission	<0.01	0.73	0.65	0.18	0.0000
Female gender	<0.01	0.73	0.66	0.18	0.0001

AIVR=accelerated idioventricular rhythm, BP=blood pressure, CVA=cerebro vascular accident, CXR=chest X-ray, Intervention=Thrombolytics, PTCA, CABG or combination, NSVT=non sustained VT, P=probability > t (multivariate), p=probability of Chi-square / Student's-T test, PPV=positive predictive accuracy, VT=ventricular tachycardia.

Bivariate analysis and multiple regression (table 6)

In 1982; 9 variables were bivariately related to in-hospital death: higher age, female gender, no smoking, signs of left ventricular dysfunction, atrial fibrillation, absence of accelerated idioventricular rhythm (AIVR), right bundle branch block, sustained ventricular tachycardia (VT), and Killip class >I. Independently related variables, identified with multiple regression were: signs of left ventricular dysfunction, atrial fibrillation, higher age, sustained VT, low systolic blood pressure on admission, Killip > 1, absence of AIVR.
In 1988; 6 variables were bivariately related to in-hospital death; dyspnea on admission, pulmonary rales, Killip class > 1, not receiving thrombolytics, PTCA or CABG, the occurrence of non sustained VT and a longer delay time before admission. When stepwise multiple regression analysis was used; Killip more than 1, absence of an intervention (thrombolytics, PTCA, CABG), and the occurrence of non sustained VT's were independently related to in-hospital death.

In 1994 bivariate analysis showed 10 variables to be related to in-hospital death: previous cerebrovascular accident, dyspnea on admission, signs of heart failure during admission, sustained VT, atrial fibrillation, female gender, no smoking, absence of an intervention, elevated creatinine on admission, a previous cardiac history. Multivariate analysis identified 5 variables independently related to in-hospital death: elevated creatinine on admission, a cardiac history, sustained VT, female gender and dyspnea on admission.

DISCUSSION

The main findings of this study are that mortality and morbidity during hospital stay improved for unselected patients admitted with myocardial infarction during the past decade and that interventions such as thrombolytic therapy, PTCA or CABG were independently related to a better outcome in 1988. There were significant differences in some baseline characteristics between the years. Patients admitted in 1994 were significantly older and more often female; also the time between onset of complaints and admission was shorter. In 1982, 75% of patients were admitted within 6 hours after the start of chest pain whereas this was 3.5 hours for the 1988 group and 2.5 hours for 1994. This earlier admission to the hospital might be related to an increased awareness by the public and health workers of the importance of urgent admission to the hospital in cases of acute chest pain. Also the finding that more patients admitted in 1988 and 1994 had previous PTCA and CABG may have increased the awareness of symptoms among individuals. It was of interest to see that significantly fewer patients of 1988 were smokers. Although it is well known that smoking increases the risk of coronary artery disease (22), we observed a better outcome after MI in smokers. Apart from the fact that non-smokers were older it may also suggest a more severe course in non-smoking individuals who still get coronary heart disease as reported previously (23).

The in-hospital mortality we found in 1982 is comparable to other studies (24,25) and the difference with 1988 and 1994 is significant. Of importance is the fact that mortality also decreased in the older age group (>70 years). This finding suggests that there will be more elderly patients with coronary heart disease in the future.

Mortality was highest in patients admitted in 1982 with anterior MI, in 1994 mortality in patients with inferior MI and right ventricular involvement was the same as for anterior MI. An even higher mortality for inferior MI with right ventricular infarction has been reported (26) As reported previously, patients with signs of left ventricular dysfunction, non-sustained VT's in the coronary care unit represent a high risk group for subsequent death in all three years (27). We also found that the absence of treatment with either

thrombolytics, PTCA or CABG was associated with a high risk for death in-hospital for our unselected patient groups of 1988 and 1994. In 1994 this variable did not reach significance in the multivariate model. Also in the present study, right bundle branch block and occurrence of VT's in the subacute phase were an indicator for pump failure and early death as previously described by our group (28), although in the multivariate model right bundle branch block did not reach significance due to the association with pump failure. Still this finding is important because of its easy recognition on the surface electrocardiogram. The occurrence of accelerated idioventricular rhythm as a sign of reperfusion (29) was independently related to a better outcome for patients admitted in 1982 and is in agreement with results of clinical trials showing a better outcome in patients with an open vessel (ref).

The use of beta-blockers, aspirin, ACE inhibitors, nitrates and calcium antagonists may have contributed to the decreased mortality although its influence is expected more after discharge.

An important variable in this study is 'eligible for thrombolytic therapy'. This variable is based on the admission ECG and the history. We found that the number of eligible patients stable throughout the study years (115 patients in 1982, 124 in 1988 and 119 in 1994). No significant differences in baseline variables were found between the 3 years. Mortality was significantly lower in 1988 and 1994. The significant decrease in mortality and morbidity can allocated to the use of thrombolytics and is in agreement with the results of clinical trials. However, only a minority of patients with MI actually receive these forms of therapy. A study reported a figure of 18% for patients receiving thrombolytic therapy (30). In 1988 and 1994 the percentage of patients receiving thrombolytics was 39% and 40%. The variable 'eligible for thrombolytic therapy' selects the ideal patient for this treatment and within this group 71% to 76% received thrombolytics in 1988 or 1994 which is in agreement with previous studies (31); the remaining patients had exclusions or reacted well on the initial treatment with heparin and nitroglycerin.

More patients admitted in the early 1980s died of an arrhythmia, whereas more patients of 1988 and 1994, died of pump failure. This change is probably due to the fact that nowadays more patients with acute MI survive the acute phase, but finally develop heart failure. However, the differences in the cause of death only show a trend but are not significant. In 1994 more patients had previous PTCA or CABG and it is expected that future MI patients will more often have a history of previous coronary heart disease, which may result in less favorable mortality figures for the total infarct population.

Limitations

The decrease in mortality over time may not only be explained by the changes in treatment but also by the changes in baseline variables; however, patients admitted during the latter years were older and more often women. Because we studied two patient cohorts admitted in the 1980s the advent of new ways of treatment after myocardial infarction such as ACE inhibition, cannot be evaluated. Therefore to answer the question whether this also led to improvement of long-term prognosis we are presently performing an analysis of the same patient cohorts after discharge.

Conclusion and implications

In three unselected patient groups admitted with acute myocardial infarction in 1982, 1988 and 1994, an improved in-hospital survival was observed in 1988 and 1994. Risk factors for in-hospital death have changed over the years with absence of a reperfusion intervention becoming an independent predictor of adverse outcome.
Whereas randomized clinical trials are of importance to prove the value of a given diagnostic or therapeutic strategy, the value of studying unselected patients over time is of importance to obtain 1) population based information (incidence, age distribution, gender differences), 2) insight into how many patients actually receive these treatments, 3) insight into mortality figures of the whole population. When these studies are repeated information is gained on changes in the MI population, changes in treatment and resulting changes in prognosis. Careful monitoring of baseline variables, changes in life style, diagnostic workup, treatment and related costs, risk stratification of the patients who need a more aggressive approach, related mortality and morbidity will lead to a better insight into the development and impact of the disease in the general population.

REFERENCES

1. Sytkowski PA, Kannel WB, D'Agostino RB. Change in risk factors and the decline in mortality from cardiovascular disease: the Framingham heart study. N Engl J Med 1990;322:1635-40.
2. Walker WJ. Changing U.S. life style and declining vascular mortality - a retrospective. N Engl J Med 1990;308:649-51.
3. Goldman L, Cook EF. The decline in ischemic heart disease mortality rates: an analysis of comparative effects of medical interventions and changes in life style. Ann Int Med 1984;101:825-36.
4. Hunt D, Sloman G, Christie D, Penington C. Changing patterns and mortality of acute myocardial infarction in a coronary care unit. Br Med J 1977;1795-8.

5. Stewart AW, Fraser J, Norris RM, Beaglehole R. Changes in severity of myocardial infarction and three year survival rates after myocardial infarction in Auckland. 1966-7 and 1981-2. Br Med J 1988;297:517-9.
6. Aberg A, Bergstrand R, Johansson S, Ulvenstam G, Vedin A, Wedel H, Wilhelmsson C, Wilhelmsen L. Declining trend in mortality after myocardial infarction. Br Heart J 1984;51:346-51.
7. Ericsson CG, Erhardt L, Rehnqvist N. Two-year survival after myocardial infarction. J Int Med 1990;227:195-9.
8. De Vreede JM, Gorgels APM, Verstraaten GMP, Vermeer F, Dassen WRM, Wellens HJJ. Did prognosis after acute myocardial infarction change during the past 30 years? A meta-analysis. J Am Coll Cardiol 1991;18:689-706.
9. Naylor CD, Chen E. Population-wide mortality trends among patients hospitalized for acute myocardial infarction: The Ontario experience, 1981 to 1991. J Am Coll Cardiol 1994;24:1431-8
10. O'Rourke RA. Overview of trends in heart disease, Changing prognosis after myocardial infarction. Ann Epidemiol 1993;3:541-6.
11. Norris RM. The changing natural history and prognosis of acute myocardial infarction. In:Rahimtoola SH, Gersh BJ, eds. New York: Elsevier. 1991:87-97.
12. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349-60.
13. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta analysis of therapeutic trials for myocardial infarction. N Engl J Med 1992;327:248-54.
14. ISIS-1 (First International Study of Infarct Survival) Collaborative group. Randomized trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. Lancet 1986;2:57-66.
15. The Multicenter Postinfarction Research Group. Risk stratification and survival after acute myocardial infarction. N Engl J Med 1983;309:331-6.
16. Stadius ML, Davis K, Maymard C, Ritchie JL, Kennedy JW. Risk stratification for 1 year survival based on characteristics identified in the early hours for acute myocardial infarction. The Western Washington Intracoronary Streptokinase Trial. Circulation 1968;74:703-11.
17. Gruppo Italiano per lo Studio della Streptochinasi Nell' infarcto Myocardio (GISSI). Effectiveness of thrombolytic therapy. Lancet 1986;i:397-402.
18. Simoons ML, Serruys PW, Van der Brand M, et al. Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. J Am Coll Cardiol 1986;7:717-28.
19. Simoons ML, Vos J, Thijssen JPG, Vermeer F, Verheugt FWA, Krauss XH, Cats VM. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. J Am Coll Cardiol 1989;14:1609-15.
20. Norusis MJ. Base Manual. SPSS Inc. Chicago, Illinois (USA) 1988.
21. SAS/STAT User's guide, version 6, fourth edition, vol 1. Cary,NC:SAS Institute Inc;1989:943.
22. Pekkanen J, Nissinen A, Puska P, Punsar S, Karvonen MJ. Risk factors and 25 year risk of coronary heart disease in a male population with a high incidence of the disease: the Finnish cohorts of the Seven countries Study. Br Med J 1989;66:7-14.
23. Molstad P. First myocardial infarction in smokers. Eur Heart J 1991;12:753-9.

24. Karlson BW, Herlitz J, Liljekvist JA, Pettersson P, Hallgren P, Strombom U, Hjalmarson A. Prognosis in Suspected Acute Myocardial Infarction in Relation to Delay Time between Onset of Symptoms and Arrival in Hospital. Cardiology 1991;78:131-7.
25. Sahasakul Y, Chaithiraphan S, Panchavinnin P, Jootar P, Thongtang V, Srivanasont N, Charoenchob N, Kangkagate C. Multivariate analysis in the prediction of death in hospital after acute myocardial infarction. Br Heart J 1990;64:182-5.
26. Zehender M, Kasper W, Kauder E, Schonthaler M, Geibel A, Olschewski M, Just H. Right ventricular infarction as an independent predictor of prognosis after acute inferior myocardial infarction. N Engl J Med 1993;328:981-8.
27. Bigger JT, Heller CA, Wenger TL, Weld FM. Risk stratification after acute myocardial infarction. Am J Cardiol 1978;42:202-10.
28. Lie KI, Wellens HJJ, Schuilenburg RM. Bundle branch block and acute myocardial infarction. In: The specific conduction system. Wellens HJJ, Lie KI, Janse MJ (Eds.) Lea and Febiger. Philadelphia 1976:662-72.
29. Gorgels APM, Vos MA, Letsch IS, Verschuuren EA, Bär FWHM, Janssen JHA, Wellens HJJ. Usefulness of accelerated idioventricular rhythm as a marker for myocardial necrosis and reperfusion during thrombolytic therapy in acute myocardial infarction. Am J Cardiol 1988;61:231-5.
30. Pashos CL, Normand STL, Garfinkle JB, Newhouse JP, Epstein AM, McNeil BJ. Trends in the use of drug therapies in patients with acute myocardial infarction. J Am Coll Cardiol 1994;23:1023-30.
31. Ellerbeck EF, Jencks SF, Radford MJ, Kresowik TF, Craig AS, Gold JA, Krumholz HM, Vogel RA. Quality of care for medicare patients with acute myocardial infarction. A four-state pilot study from the cooperative cardiovascular project. JAMA 1995;273:1509-14.

CHAPTER 4

No Change in One Year Mortality in Patients Discharged After an Acute Myocardial Infarction

Observations From 1982 to 1994

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ABSTRACT

In recent years the effect on mortality of various new treatments in acute myocardial infarction (MI) has been well documented using randomized controlled studies in selected patient groups. However, the impact of these changes in treatment on unselected patient groups is largely unknown. The purpose of this study was to investigate the effect of changes in treatment strategies in relation to first year morbidity and mortality in unselected patients admitted to the hospital because of an acute MI.

We studied all patients admitted to the department of cardiology of the academic hospital of Maastricht (the Netherlands) with acute myocardial infarction (MI) in the years 1982, 1988 and 1994. Information on incidence, baseline characteristics, clinical variables and interventions was collected and related to follow-up data such as readmissions, morbidity and mortality.

In the study years 223, 227 and 235 patients were admitted with an acute MI. The total population of the study area increased from 172,702 in 1982 to 178,973 in 1988 and 182,185 in 1994. The incidence of first MI was 0.12%, 0.13% and 0.13% respectively with an increase in the age group over 80; 0.24%, 0.36% and 0.36% respectively. Patients admitted in 1994 were older, more often female and had less often a previous MI. A decrease of the number of smokers was observed. Also hospital delay time decreased over the years. More patients admitted in 1994 had previous percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG). In-hospital mortality was 38 (17%) in 1982, 23 (10%) in 1988 and 22 (9%) in 1994. ($p<0.05$). Mortality after one year was 13 (6%) in 1982, 12 (5%) in 1988 and 14 (7%) in 1994. Variables related to high risk for dying during follow-up for all years were the occurrence of right bundle branch block within 48 hours after admission, age above seventy, Killip class more than I on admission, dyspnoea functional class more than I at discharge, anterior MI and not receiving aspirin.

Conclusion: while in-hospital mortality decreased, the one-year mortality after discharge for unselected patients admitted with an acute MI remained the same during more than a decade despite the introduction of various new treatment modalities and increased ageing of the infarct population.

INTRODUCTION

Coronary heart disease is the major cause of death in the majority of the industrialized countries including the Netherlands (1,2).
The mortality rate from coronary heart disease decreased steadily during the past decades in most countries (3). This reported decline in mortality may be explained by a decreased incidence because of changes in life style (diet, smoking, exercise) resulting in a decrease in risk factors, better pharmacological control of hypertension, and/or by better treatment of the acute and chronic stage of ischemic heart disease. (4-10). The in-hospital outcome of patients admitted with acute myocardial infarction (MI) has been the subject of many studies during the past 30 years. A meta-analysis from our group and data from other studies showed that the hospital outcome improved during the 1960's, 1970's and 1980's (3,11). The purpose of the present study was to investigate changes in baseline characteristics and modes of treatment in relation to changes in one-year outcome of patients discharged after an acute MI.

METHODS

The study was performed at the department of cardiology of the Academic Hospital of Maastricht, the Netherlands. This is the only hospital in an area with at present approximately 182,000 inhabitants and therefore serves as a primary hospital for acute ischemic heart disease. The hospital records of all patients admitted in 1982, 1988 and 1994 with acute myocardial infarction were reviewed.
The admission diagnosis of acute MI was made if there was a history of typical chest pain of more than 30 minutes duration, accompanied by ST-segment elevation of more than 0.1 mV in at least one extremity lead or two adjoining precordial leads. Right ventricular involvement in patients with an inferior MI was diagnosed when ST-segment elevation was present equal to or more than 0.1 mV with a positive T-wave in the right precordial lead V4. In patients with a recurrent MI the same criteria were required. Extension of an old MI was diagnosed, apart from QRS-changes, by increased ST-segment elevation compared to the most recent electrocardiogram after the previous MI. Patients presenting with either left or right bundle branch block were also included if the history was suggestive of MI and the diagnosis confirmed by typical enzyme changes. No secondary or tertiary referral patients were included. Age or previous medical history were no reason for exclusion.
A final diagnosis of MI was made if there was a typical rise of aspartate aminotransferase above the upper limit of normal (40 Units per liter).

Baseline characteristics on admission and variables regarding medical and invasive treatment were collected and related to one-year mortality and morbidity.

Statistical analysis

The data were analysed by using the Statistical Package of the Social Sciences (12) and the SAS program (13).
Bivariate analysis was performed with Student t-test to compare groups with continuous variables and chi-square for groups with discrete variables. To correct for cells with an expected count less than 5, the likelihood ratio Chi-square was used and Fisher's exact test. P-values less than five percent were considered statistically significant. Variables reaching significance in the bivariate analysis together with other relevant variables were used in a multiple regression analysis. For these variables also sensitivity, specificity and positive predictive accuracy were calculated. The independent importance of different variables was calculated for death during one-year follow-up. The methods were unchanged throughout the follow-up.
Data are presented as mean $\pm$ standard deviation.

RESULTS

Baseline characteristics

In the study years there was an increase in the total population of the region of Maastricht from 172,702 in 1982 to 178,973 in 1988 to 182,185 in 1994. The incidence of first MI remained the same: 0.12%, 0.13% and 0.13% respectively. However there was an increased incidence in the age group over 80 years: 0.24%, 0.36% and 0.36% respectively.
Table 1 shows demographic characteristics of all patients admitted with MI. In 1982, 223; in 1988, 227 and in 1994, 235 patients were admitted with an acute MI. At baseline patients admitted in 1994 were significantly older. In 1982, 125 had inferior MI (33 with right ventricular involvement) and 98 had anterior MI. In 1988 there were 146 with inferior MI (49 right ventricular involvement) and 81 with anterior MI. In 1994, 148 had inferior MI (50 with right ventricular involvement) and 87 had anterior MI. Table 1 also shows that differences were found for delay time between onset of symptoms and the admission time, smoking, and gender. Patients admitted in 1994 had significantly more frequent previous PTCA or CABG as compared to 1982.
Drug treatment at discharge and during follow-up varied markedly between the years (Table 2). There was a decrease in the prescription of coumarins in favor of the prescription of aspirin. Over the years more drug were used to prevent pump failure and less drugs to treat pump failure (diuretics, digoxin).

Table 1. Baseline characteristics and interventions of patients with MI in 1982, 1988, 1994.

	1982		1988		1994	
N	223		227		235	
age (mean ± SD)*	64.8 ± 11.1		63.9 ± 12.1		66.2 ± 11.2	
male *	151	(68)	166	(73)	146	(62)
smoking *	135	(61)	108	(48)	114	(48)
diabetes	33	(15)	27	(12)	21	(9)
hypertension	89	(40)	75	(33)	84	(36)
previous infarction	62	(28)	52	(23)	49	(21)
previous PTCA *	0		2	(1)	11	(5)
previous CABG *	3	(1)	12	(5)	13	(6)
75% admitted within *	6 hours		3.5 hours		2.5 hours	
thrombolytics *	3	(1)	62	(27)	68	(29)
thrombolytics + rescue PTCA *	0		27	(12)	25	(11)
primary PTCA *	0		10	(4)	26	(11)
late thrombolytics *	0		10	(4)	6	(3)
late PTCA *	1	(.4)	18	(8)	59	(25)
CABG *	0		11	(5)	18	(8)

* p is at least <.05, CABG=coronary artery bypass grafting, PTCA=balloon angioplasty, SD=standard deviation, Percentages between brackets.

Table 2. Drugs at discharge, and after one year follow-up. Figures are percentages.

	discharge			follow-up		
	1982	1988	1994	1982	1988	1994
Beta blockers	29	53	58	35	42	66
Nitrates	79	50	73	60	30	70
Calcium antagonists	28	46	23	25	41	31
Ace inhibitors	0	10	24	1	12	27
Diuretics	59	19	16	43	22	23
Digoxin	46	10	10	33	9	8
Aspirin	5	73	72	6	60	80
Coumarins	37	19	16	27	18	16

Table 3. One-year follow-up data of patients discharged after myocardial infarction

	1982	%	1988	%	1994	%
	n=185		n=204		n=213	
Readmission cardiology*	66	36	42	21	35	16
Reinfarction*	15	8	10	5	4	2
PTCA*	2	1	5	2	11	5
CABG	9	5	9	4	13	6
AP FC I*	103	56	139	68	173	81
Dyspnea FC 1	136	74	148	73	170	80
Death	13	7	12	6	14	6

PTCA=percutaneous transluminal coronary angioplasty, CABG=coronary arterial bypass grafting, AP FC I=Angina pectoris functional class 1. *p<.05.

Table 4. Causes of death

	1982 n=13	1988 n=12	1994 n=14
arrhythmic	3	2	2
recurrent infarct	3	2	1
pump-failure	4	5	7
other cardiac	1	1	1
non cardiac	2	2	3

Table 5. Variables of prognostic importance for death during one-year follow-up of patients discharged in 1982, 1988 and 1994; multiple regression analysis.

Variable	Relative Risk	95% Confidence interval
Right bundle branch block	3.19	1.13 - 8.93
Killip class > I	2.82	1.10 - 7.19
Age > 70 years	2.56	1.12 - 5.86
Not receiving Aspirin	3.42	1.42 - 8.18
Dyspnea FC>I at discharge	3.82	1.60 - 9.10

Only a few patients admitted in 1982 underwent an invasive intervention whereas in 1988, 62 (27%) received thrombolytics, 27 (12%) thrombolytics and rescue PTCA, 10 (4%) acute PTCA, 18 (8%) late PTCA (defined as PTCA in the subacute phase or at a new episode during the same admission) and 11 (5%) CABG.
In 1994, 68 (29%) received thrombolytics, 25 (11%) thrombolytics followed by PTCA, 26 (11%) acute PTCA, 59 (25%) late PTCA and 18 (8%) CABG (table 1).
In 1982, 38 (17%) patients died in hospital and 13 (6%) during one year follow-up. In 1988, 23 (10%) patients died in hospital and 12 (5%) during follow-up and in 1994, 22 (9%) patients died in hospital and 14 (7%) during follow-up (table 2).
During the follow-up period of one year less patients discharged in 1988 or 1994 required readmissions, also less reinfarctions were observed in these patients, although they underwent more often a PTCA. CABG during follow-up was equally divided for all three years. Morbidity as assessed by the functional class of angina or dyspnea according to the criteria of the New York Heart Association showed that less patients discharged in 1988 or 1994 had anginal complaints during follow-up. No change in complaints of dyspnoea was observed (Table 3).
The causes of death are listed in table 4. It is shown that the most frequent cause of death seems to be pump failure in all three years although no significant differences in causes of death were observed.
Multivariate analysis with stepwise multiple logistic regression identified six variables related to death during follow-up when the three years were combined: age above 70 years, Killip class more than one, the occurrence of right bundle branch block within 48 hours after admission, dyspnea functional class more than one, anterior MI and no prescription of aspirin (table 5).

DISCUSSION

The main findings of this study are that although hospital mortality decreased significantly during a period of more than a decade, one-year mortality after discharge remained the same in patients admitted with an acute MI. During the study years there was a change in baseline variables such as an increased age and a higher incidence of previous coronary interventions in recent years (table 1). Despite the fact that mortality after discharge remained the same, patients admitted in 1988 and 1994 do better after discharge in terms of anginal complaints, reinfarctions and readmissions. This improvement in morbidity is achieved at the costs of more interventions and the use of more drugs. As far as we know, a similar study comparing one-year outcome in unselected patient groups before and

after the introduction of new methods for coronary reperfusion has not been done before. The mortality figures (7% in 1982, 6% in 1988 and 6% in 1994) are relatively high in comparison to previously published data possibly due to the fact that we studied unselected patients of all ages. Studies reporting on one-year mortality of patients treated with thrombolysis show figures averaging from 2.2%-7.2% (14).

The reinfarction rate decreased significantly during the study years from 8% in 1982 to 5% in 1988 and 2% in 1994. Our data from 1982 and 1988 correspond with previously published data showing reinfarction rates of approximately 5%, however most of these data are from selected patient groups before the thrombolytic era (15). At present no data are available concerning first year reinfarction rates in unselected patients with MI in the 'reperfusion age'.

Certain risk factors that we found to be indicative for an unfavorable course after MI have been reported before such as signs of dyspnoea or a Killip class more than I (16,17). The observation that receiving aspirin improved prognosis should be regarded with caution because treatment was based on clinical indication rather than randomization and the better outcome in the treated subgroup cannot be attributed only to the beneficial effect of the drug. Also specific contraindications in the group not receiving the drug were not registered.

As is well known for many years both the presence of right bundle branch block as well as the anterior location of the infarction were associated with increased one-year mortality (18,19). Also this study shows that right bundle branch block is an independent predictor.

Invasive interventions that were introduced during the 1980's improved the hospital outcome in MI patients but did not influence one-year mortality. However, the effect of new drugs such as ACE inhibitors and lipid lowering drugs may change long-term outcome. It will be of great interest to evaluate these effects in future studies.

REFERENCES

1. Weijenberg M. Prospective studies on coronary heart disease in the elderly. Thesis Wageningen, The Netherlands, 1996
2. Nederlandse Hartstichting. Hart- en vaatziekten in Nederland 1995. Cijfers over ziekte en sterfte. Den Haag: Nederlandse Hartstichting, 1995. (in Dutch).
3. De Vreede JJM, Gorgels APM, Verstraaten GMP, Vermeer F, Dassen WRM, Wellens HJJ. Did prognosis after acute myocardial infarction change during the past 30 years? A meta-analysis. J Am Coll Cardiol 1991;18:698-706.
4. Sytkowski PA, Kannel WB, D'Agostino RB. Change in risk factors and the decline in mortality from cardiovascular disease: the Framingham heart study. N Engl J Med 1990;322:1635-40.

5. Walker WJ. Changing U.S. life style and declining vascular mortality - a retrospective. N Engl J Med 1990;308:649-51.
6. Goldman L, Cook EF. The decline in ischemic heart disease mortality rates: an analysis of comparative effects of medical interventions and changes in life style. Ann Int Med 1984;101:825-36.
7. Hunt D, Sloman G, Christie D, Penington C. Changing patterns and mortality of acute myocardial infarction in a coronary care unit. Br Med J 1977;1795-8.
8. Stewart AW, Fraser J, Norris RM, Beaglehole R. Changes in severity of myocardial infarction and three year survival rates after myocardial infarction in Auckland. 1966-7 and 1981-2. Br Med J 1988;297:517-9.
9. Aberg A, Bergstrand R, Johansson S, Ulvenstam G, Vedin A, Wedel H, Wilhelmsson C, Wilhelmsen L. Declining trend in mortality after myocardial infarction. Br Heart J 1984;51:346-51.
10. Ericsson CG, Erhardt L, Rehnqvist N. Two-year survival after myocardial infarction. J Int Med 1990;227:195-9.11.Naylor CD, Chen E. Population-wide mortality trends among patients hospitalized for acute myocardial infarction: The Ontario experience, 1981 to 1991. J Am Coll Cardiol 1994;24:1431-8.
12. Norusis MJ. Base Manual. SPSS Inc. Chicago, Illinois (USA) 1988.
13. SAS/STAT User's guide, version 6, fourth edition, vol 1. Cary,NC:SAS Institute Inc;1989:943.
14. O'Rourke RA. Overview of trends in heart disease, changing prognosis after myocardial infarction. Ann Epidemiol 1993;3:541-6.
15. Kornowski R, Goldbourt U, Zion M, Mandelzweig MPH, Kaplinsky E, Levo Y, Behar S, and the SPRINT Study Group. Am J Cardiol 1993;72:883-8.
16. O'Rourke RA. Clinical decisions in post infarction patients. Mod Concept Cardiovasc Dis. 1986;55:55-60.
17. Gadsboll N, Hoilund-Carlsen PF, Madsen EB, Marving J, Pedersen A, Lonborg-Jensen H, Dige-Petersen H, Jensen BH. Right and left ventricular ejection fractions: Relation to one-year prognosis in acute myocardial infarction. Eur Heart J 1987;8:1201-9.
18. Lie KI, Wellens HJ, Schuilenberg RM, et al. Factors influencing prognosis of bundle branch block complicating acute antero-septal infarction. The value of His bundle recordings. Circulation 1974;50:935-41.
19. Ricou F, Nicod P, Gilpin E, Henning H, Ross J. Influence of right bundle branch block on short- and long-term survival after acute anterior myocardial infarction. J Am Coll Cardiol 1991;17:858-63.

CHAPTER 5

Evidence of Improved Long-Term Outcome After Acute Myocardial Infarction

Observations in Unselected Patients

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Submitted for publication

ABSTRACT

In recent years the mortality of acute myocardial infarction (MI) has decreased, either because of a lower incidence of MI and/or because of a decrease in fatality rate. The former may have changed as a result of primary prevention. The latter may be the result of various new treatments that have become available during the past decade. In this study we evaluated the role of treatment changes in an unselected patient group from the area of Maastricht (The Netherlands) with emphasis on long-term outcome.

All patients admitted with acute MI in 1982 and 1988 were included in the study. Information on baseline characteristics, clinical variables and all interventions during hospital stay and five-year follow-up was collected. In those two years 223 and 227 patients were admitted because of an acute MI. More patients admitted in 1988 had previous balloon angioplasty and coronary bypass grafting. Smoking habits decreased during the past decade. Five-year mortality was 54 (29%) for patients of 1982 and 39 (19%) for patients of 1988 ($p<0.05$). Multiple logistic regression analysis with the year of admission in the model identified 7 variables related to death during five-year follow-up for 1982 and 1988: diabetes mellitus, the occurrence of right bundle branch block during admission, age above 70, previous MI, peripheral vascular disease, diminished left ventricular function and no percutaneous transluminal coronary angio-plasty (PTCA) or coronary artery bypass grafting (CABG) during follow-up.

Conclusion: Five-year mortality after discharge for unselected patients admitted with an acute MI decreased between 1982 and 1988. The incidence of first MI remained the same during the study period.

INTRODUCTION

The reported decline in mortality from coronary heart disease may be due to a decreased incidence, a decreased fatality rate or both. The former may be the result of changes in life style resulting in a decrease in risk factors, better control of hypertension; the latter because of a more benign course of the disease, changing patient profile and better modes of treatment in the acute and chronic stage of ischemic heart disease (1-7). A decreased incidence of myocardial infarction (MI) has actually been reported (8,9). As far as the profile of the patients admitted with acute MI is concerned we recently reported that patients with acute MI admitted during the past decade increased in age and had more coronary interventions before admission in the recent years (10).

As far as mortality is concerned, a meta-analysis done by our group suggested that in unselected infarct patients admitted between 1960 and 1980, short-term prognosis improved but that after discharge the long-term outcome remained constant (11). Data concerning long-term follow-up of patients admitted in the thrombolytic era are available but usually restricted to patients selected for clinical trials (12,13). Furthermore it is of importance to evaluate changes in population characteristics over the years with their possible effects on mortality.

The purpose of this paper is to present data on time related changes in the incidence, modes of treatment and their effects on long-term mortality and morbidity after acute MI by examining five-year follow-up data of the years 1982 and 1988.

METHODS

The study was performed at the department of cardiology of the Academic Hospital of Maastricht, the Netherlands. This is the only hospital in an area with approximately 182,000 inhabitants and serves therefore in this area as the primary hospital for acute ischemic heart disease. Following discharge all patients are controlled in the out-patient clinic. The hospital records and out-patient data of all patients admitted in 1982 and 1988 with myocardial infarction (MI) were reviewed.

The admission diagnosis of acute MI was made if there was a history of typical chest pain of more than 30 minutes of duration, accompanied by ST-segment elevation of more than 0.1 mV in at least one extremity lead or precordial lead. Right ventricular involvement in patients with an inferior MI was diagnosed when ST-segment elevation was present equal to or more than 0.1 mV with a positive T-wave in the right precordial lead V4. In patients with a recurrent MI the same criteria were required. Extension of an old MI was diagnosed, by new ST-segment elevation compared to the most recent

electrocardiogram after the previous MI. Patients presenting with either left or right bundle branch block were also included if the history was suggestive of MI and the diagnosis confirmed by typical plasma enzyme changes. No secondary or tertiary referral patients were included. Age or previous medical history were no reason for exclusion.
A final diagnosis of MI was made if there was a typical rise of aspartate aminotransferase above the upper limit of normal (40 Units per liter). Also creatine kinase and lactic dehydrogenase had to be elevated. Clinical variables were collected with emphasis on medical and invasive treatment. The use of various medications was registered on admission and during hospital stay. All interventions such as thrombolytic therapy, PTCA and CABG were registered. To calculate the incidence of first MI we obtained age-adjusted population data from the central office of statistics of the Netherlands (CBS).

Statistical analysis

The data were analyzed by using the Statistical Package of the Social Sciences (14) and the SAS program (15).
Bivariate analysis was performed with Student t-test to compare groups with continuous variables and chi-square for groups with discrete variables. To correct for cells with an expected count less than 5, the likelihood ratio chi-square was used and Fisher's exact test. Variables reaching significance in the bivariate analysis together with other relevant variables were used in a multiple regression analysis. The independent importance of different variables was calculated for death during five-year follow-up.
Data are presented as mean $\pm$ standard deviation.

RESULTS

Baseline characteristics

Table 1 shows demographic characteristics of all patients. The number of patients remained grossly the same in the two study years; in 1982, 223 and in 1988, 227 were admitted with an acute MI. Figure 1 shows the incidence of first MI for every age group in our region. It indicates that the incidence remained the same for the whole population (1982: 12/10,000, 1988: 13/10,000), although there was an increase in the population above eighty (1982: 24/10,000, 1988: 36/10,000). Table 1 shows that differences were found for delay time between onset of symptoms and the admission time and smoking. While in 1982 seventy five percent of patients were admitted within 6 hours this shortened to 3.5 hours in 1988 ($p<0.05$). Smoking was less frequent in 1988 (48% vs 61% in 1982; $p<0.01$).

Table 1. Baseline characteristics and interventions of patients with MI in 1982 and 1988.

	1982		1988	
N	223		227	
age (mean ± SD)*	64.8 ±11.1		63.9 ±12.1	
<70 years *	139	(62)	157	(69)
male	151	(68)	166	(73)
smoking *	135	(61)	108	(48)
diabetes	33	(15)	27	(12)
hypertension	89	(40)	75	(33)
previous infarction	62	(28)	52	(23)
previous PTCA	0		2	(1)
previous CABG	3	(1)	12	(5)
75% admitted within *	6 hours		3.5 hours	
thrombolytics *	3	(1)	62	(27)
thrombolytics + rescue PTCA *	0		27	(12)
primary PTCA *	0		10	(4)
late thrombolytics *	0		10	(4)
late PTCA *	1	(.4)	18	(8)
CABG *	0		11	(5)

* p is at least <0.05, CABG=coronary artery bypass grafting, PTCA=percutaneous transluminal coronary angioplasty, SD=standard deviation, Percentages between brackets.

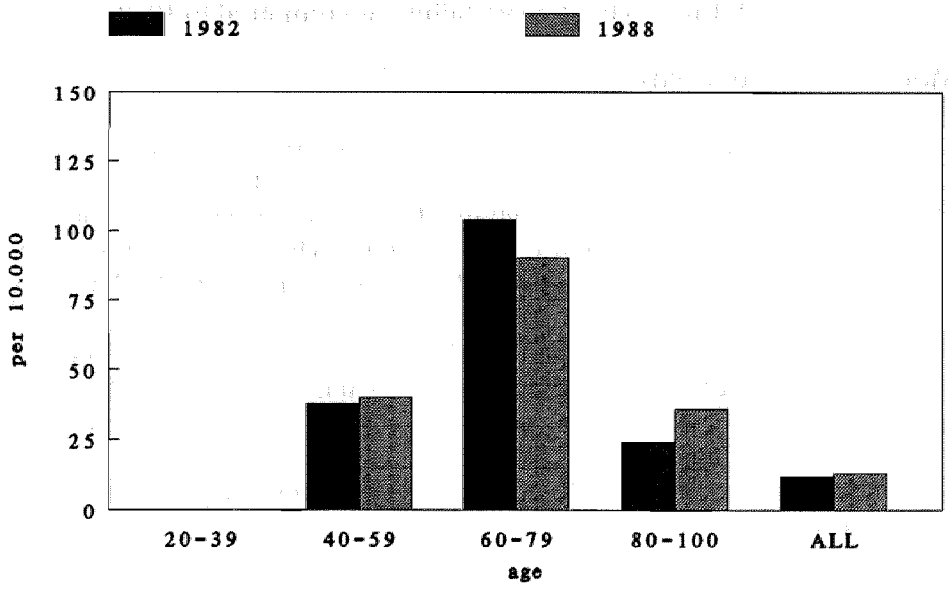

Figure 1. Incidence of MI in different age groups for the region of Maastricht.

Table 2. Drugs on discharge, and during follow-up in 1982 and 1988. Figures are percentages. For all drugs there is a significant difference in the number of prescriptions between the years.

	1982		1988	
	discharge	5-year (131)	discharge	5-year (165)
Beta blockers	29	54	53	61
Nitrates	79	86	50	54
Aspirin	5	13	73	111
Calcium ant.	28	41	46	77
Diuretics	59	61	19	14
Coumarins	37	38	19	27
Ace inhibitors	0	6	10	31
Digoxin	46	44	10	13

Also initial treatment changed significantly, more patients of the latter year received thrombolytic therapy, balloon angioplasty or coronary bypass grafting.

As shown in table 2, oral drug treatment at discharge and during follow-up varied significantly between the years, reflecting new insights because of the results of clinical trials with various new drugs but probably also as a result of changes in the evolution of the disease. During follow-up of the 1988 patients, more received drugs to prevent heart-failure and angina pectoris and less received drugs to treat heart-failure as compared to 1982.

Morbidity and mortality

Morbidity was assessed in terms of angina pectoris and dyspnea during follow-up according to the criteria of the New York Heart Association. As shown in table 3, of the patients discharged in 1988 more had angina pectoris functional class 1 at follow-up (70% versus 54%). However dyspnea functional class 1 was the same after five years for patients discharged in 1982 and 1988.

Readmission rates decreased significantly; of the patients discharged in 1982, 61% were readmitted for cardiac reasons while this was 45% for those discharged in 1988. Reinfarction occurred less often in those discharged in 1988 (10%) than those in 1982 (22%).

More interventions (PTCA/CABG) were done in patients discharged in 1988 (1982: 14%, 1988 25%).

Table 3. Five-year follow-up data of patients discharged after myocardial infarction

	1982 n=186	%	1988 n=204	%
Number of readmitted patients *	113	61	92	45
Number of reinfarctions *	40	22	20	10
PTCA *	4	2	21	10
CABG	23	12	31	15
AP FC I *	101	54	144	70
Dyspnea FC 1	124	67	131	64
Death *	54	29	39	19

PTCA=percutaneous transluminal coronary angioplasty, CABG=coronary arterial bypass grafting, AP FC I=Angina pectoris functional class 1. *p<0.05 Between 1982 and 1988.

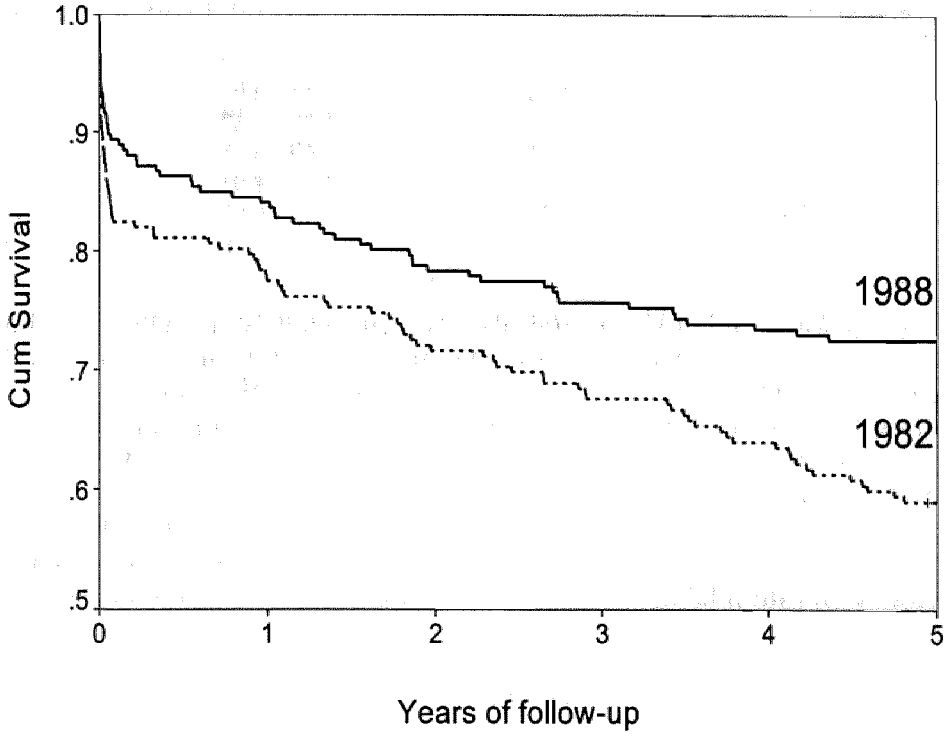

Figure 2. 5-year survival of patients with acute MI admitted in 1982 or 1988. Wilcoxon test for equality of survival curves (p<.05).

Table 4. Causes of death (percentages between brackets).

	1982 n=54	%	1988 n=39*	%
arrhythmic	13	24	5	13
recurrent infarct	12	22	7	18
pump-failure	14	26	13	33
other cardiac	2	4	2	5
non cardiac	13	24	12	31

* $p<0.05$ difference in total mortality between 1982 and 1988

Table 5. Variables of prognostic importance for death during five-year follow-up of patients discharged in 1982 and 1988; multiple regression analysis.

Variable	Relative Risk	95% Confidence interval
Diabetes	3.33	1.96 - 7.87
Right bundle branch block	2.37	1.16 - 4.82
Age > 70 years	2.88	2.14 - 3.87
Previous infarction	1.78	1.25 - 2.53
Peripheral vascular disease	3.41	2.08 - 5.58
Heart failure	2.20	1.60 - 3.01
No PTCA or CABG	2.46	2.04 - 4.05

Figure 2 shows Kaplan Meier survival curves with a follow-up of five years for the 1982 and 1988 patients. In-hospital mortality was 17% and 10% ($p<0.05$) respectively. One-year mortality for both years was the same. Five year mortality after discharge was 54 (29%) for the 1982 group and 39 (19%) ($p<0.05$) for the 1988 group. The figure shows that the differences in survival occur late after MI.

The causes of death are listed in table 4. It shows that the most frequent cause of death was pump-failure. However there was an increase in patients dying from pump failure (26% and 33%) and a decrease in the number of arrhythmic deaths (24% and 13%).

As shown in table 5, with multiple logistic regression analysis, seven variables were identified which were related to death during five years of follow-up after MI with the year of admission included in the regression analysis together with all significant and relevant variables. These variables were: diabetes mellitus (RR 3.33 CI 1.96-7.87), right bundle branch block (RR 2.37 CI 1.16-4.82), previous MI (RR 1.78 CI 1.25-2.53), peripheral vascular disease (RR 3.41 CI 2.08-5.58), signs of heart failure (RR 2.20 CI 1.60-3.01) and age above seventy (RR 2.88 CI 2.14-3.87). Not receiving balloon angioplasty or coronary bypass grafting during follow-up was also associated with death

after correction for age and pumpfailure and known risk factors (RR 2.46 CI 2.04-4.05).

DISCUSSION

This study demonstrates that five-year mortality and morbidity improved for unselected patients discharged after acute MI. This difference became evident only after 2.5 years, indicating that in these patients studies with a long follow-up time are required to demonstrate changes in mortality. It also suggests that secondary preventive measures after MI show their benefit not in the immediate post-infarction period. To the best of our knowledge, this is the first report to show a declined five-year mortality in unselected patients after acute MI in the thrombolytic era. The difference in mortality is even more striking when we take into account that the incidence of acute MI remained the same. One has to be careful however in the interpretation of data concerning the incidence of a disease over time. Changes in demographic characteristics, coding of disease and diagnostic accuracy may occur. However the two patient groups were studied, by the same investigators using the same criteria. In contrast to other studies, we found no change in the overall incidence of MI. (8,9). We did observe a decline of the MI incidence in the age group below 80 and an increase in the older population. In the 1960s and the 1970s five-year mortality after MI remained constant around 33% (11). Data on long-term mortality in the thrombolytic era are rare and frequently reporting on selected patients. Stevenson et al. report a three-year mortality of 29.4%. In that patient group only 38% was using B-Blockers, possibly reflecting the relatively high incidence of contraindications (16).

McGovern et al. found a three-year mortality in patients below 75 years admitted in 1985 of 16% in men and 22% in women (9). For those admitted in 1990, the three year mortality was 12% in men and 18% in women. These data approximate our findings of a five-year mortality of 19% for those admitted in 1988. A low five-year mortality of 12.6% has been observed in selected patients treated with thrombolytic therapy in the Netherlands (12). Variables related to death during five-year follow-up for the 1982 and 1988 patients were diabetes mellitus, the occurrence of right bundle branch block during admission, age above 70, previous MI, peripheral vascular disease, diminished left ventricular function and no PTCA during follow-up. Many of these risk factors have been described previously and they are still of importance to stratify patients on admission or at discharge into a high risk group frequently requiring a more aggressive treatment (17-21). However, in contrast to previous reports we found that peripheral vascular disease was an independent predictor of long-term mortality. Apart from an effect on hospital mortality, Behar et al (22) observed in their study no independent

contribution of peripheral vascular disease on long-term mortality, possibly related to the fact that they only included patients with a first MI. Also in comparison to our cohort they had less patients who were smoking. Although single high risk variables can identify individuals with an adverse outcome, they do not fully explain the differences in mortality between the patient cohorts. The improved long-term survival is multifactorial. In the general population there is an increased awareness of the importance of risk factors which is reflected in decreased smoking habits in our patient cohorts over the years. Earlier admission to the hospital in case of MI is the result of better information to the public and the fact that more patients nowadays have a previous history of balloon angioplasty and bypass grafting making them knowledgeable what to do in case of acute chest pain. Treatment of hypertension, diabetes and hyperlipidemia is more intense and patients with known coronary heart disease are treated with a variety of drugs such as beta-blockers, aspirin, ACE-inhibitors and lipid lowering drugs. In hospital treatment changed as a result of clinical trials leading to early reperfusion strategies.

After discharge rehabilitation programs focus on physical fitness, risk factor reduction and psychological factors. Also drugs for secondary prevention such as aspirin, beta-blockers, ace-inhibitors and lipid lowering drugs are routine unless contraindicated. Furthermore patients with high risk variables after discharge such as recurrent arrhythmias, recurrent chest pain or progressive deterioration of left ventricular function are identified and treated more aggressively. It is obvious that all these factors contribute to the improved long-term survival. A recent study by Hunink showed that most of the decline in CHD mortality in the US can be explained by secondary prevention (23).

Not only long-term mortality decreases as a result of all these measures but there will also be a reduction in recurrent angina pectoris and reinfarction resulting in less readmissions for cardiac reasons. However, in view if the ageing of the population we speculate that the improved long-term survival and lower readmission rate may ultimately change because of the increasing number of elderly survivors having more co-morbidity and poorer left ventricular function.

REFERENCES

1. Sytkowski PA, Kannel WB, d'Agostino RB. Change in risk factors and the decline in mortality from cardiovascular disease: The Framingham heart study. N Engl J Med 1990;322:1635-40.
2. Walker WJ. Changing U.S. life style and declining vascular mortality - a retrospective. N Engl J Med 1990;308:649-51.

3. Goldman L, Cook EF. The decline in ischemic heart disease mortality rates: an analysis of comparative effects of medical interventions and changes in life style. Ann Int Med 1984;101:825-36.
4. Hunt D, Sloman G, Christie D, Penington C. Changing patterns and mortality of acute myocardial infarction in a coronary care unit. Br Med J 1977;1795-8.
5. Gruppo Italiano per lo Studio della Streptochinasi Nell' infarcto Myocardio (GISSI). Effectiveness of thrombolytic therapy. Lancet 1986;i:397-402.
6. Simoons ML, Serruys PW, Van der Brand M, et al. Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. J Am Coll Cardiol 1986;7:717-28.
7. Second International Study of Infarct Survival (ISIS-2) Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. Lancet 1988;II:349-60.
8. Goldberg RJ, Gorak EJ, Yarzebski J, Hosmer DW, Dalen P, Gore JM, Alpert JS, Dalen JE. A communitywide perspective of sex differences and temporal trends in the incidence and survival rates after acute myocardial infarction and out-of-hospital deaths caused by coronary heart disease. Circulation 1993;87:1947-53.
9. McGovern PG, Pankow JS, Shahar E, Doliszny KM, Folsom AR, Blackburn H, Luepker RV, For the Minnesota Heart Survey Investigators. Recent trends in acute coronary heart disease. Mortality, Morbidity, medical Care, and Risk Factors. N Engl J Med 1996;334:884-90.
10. Widdershoven JWMG, Gorgels APM, Vermeer F, Dijkman LWN, Dassen WRM, Wellens HJJ. Changes in characteristics and in-hospital outcome of patients admitted with acute myocardial infarction, observations from 1982 to 1994. Eur Heart J 1996;17:560 (abstract).
11. De Vreede JJM, Gorgels APM, Verstraaten GMP, Vermeer F, Dassen WRM, Wellens HJJ. Did prognosis after acute myocardial infarction change during the past 30 years? A meta-analysis. J Am Coll Cardiol 1991;18:689-706.
12. Simoons ML, Vos J, Thijssen JPG, Vermeer F, Verheugt FWA, Krauss XH, Cats VM. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. J Am Coll Cardiol 1989;14:1609-15.
13. Taylor GJ, Sang A, Korsmeyer C, et al. Six year survival after thrombolysis for acute myocardial infarction, Circulation 1989;80:520.
14. Norusis MJ. Base Manual. SPSS Inc. Chicago, Illinois (USA) 1988.
15. SAS/STAT User's guide, version 6, fourth edition, vol 1. Cary,NC:SAS Institute Inc;1989:943.
16. Stevenson R, Ranjadaylan K, Wilkinson P, Roberts R, Timmis AD. Short and long term prognosis of acute myocardial infarction since introduction of thrombolysis. Br Med J 1993;307:349-53.
17. Goldberg RJ, Gore JM, Gurwitz JH, Alpert JS, Brady P, Strosnitter W, Chen Z, Dalen JE. The impact of age on the incidence and prognosis of initial acute myocardial infarction: The Worcester Heart Attack Study. Am Heart J 1989;117/3:543-9.
18. Ricou F, Nicod P, Gilpin E, Henning H, Ross J. Influence of right bundle branch block on short- and long-term survival after acute myocardial infarction. J Am Coll Cardiol 1991;17:858-63.
19. Wong ND, Cupples LA, Ostfeld AM, Levy D, Kannel WB. Risk factors for long-term coronary prognosis after initial myocardial infarction: The Framingham study. Am J Epidemiol 1989;130:469-80.

20. Castello R, Alegria E, Merino A, Malpartida F, Martinez-Caro D. Effect of age on long-term prognosis of patients with myocardial infarction. Int J Cardiol 1988;20:221-30.
21. Kambara H, Nakagawa M, Kinishita M, Kawai C. Long-term prognosis after myocardial infarction: Univariate and multivariate analysis of clinical characteristics in 1000 patients. Clin Cardiol 1993;16:872-8.
22. Behar S, Zion M, Reicher-Reiss H, Kaplinsky E, Goldbourt U, for the SPRINT Study Group. Short- and long-term prognosis of patients with a first acute myocardial infarction with concomitant peripheral vascular disease. Am J Med 1994;96:15-9.
23. Hunink MGM, Goldman L, Tosteson ANA, Mittleman MA, Goldman PA, Williams LW, Tsevat J, Weinstein MC. The recent decline in mortality from coronary heart disease, 1980 - 1990. The effect of secular trends in risk factors and treatment. JAMA 1997;277:535-42.

CHAPTER 6

Improved Outcome In-Hospital and During Follow-up of Patients Admitted with Unstable Angina Pectoris Early and Late in the Eighties

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ABSTRACT

The purpose of this study was to investigate whether prognosis in-hospital and during long-term follow-up of patients admitted with unstable angina pectoris (UAP) has changed during the 1980's.

Design: Comparison of in-hospital and 5-year follow-up data of patient cohorts of 1982 and 1988 admitted with UAP to a single hospital in an area with approximately 182,000 inhabitants. Patients: Consecutive patients of all ages admitted with UAP. Follow-up was completed in 98%. Main Outcome: 5-year mortality and morbidity of patients admitted with UAP.

In 1982, 258 patients were admitted with UAP. During hospital stay, 10 patients underwent coronary artery bypass grafting (CABG) and 1 percutaneous transluminal coronary angioplasty (PTCA). Myocardial infarction developed in 79 (31%) patients and 3 (1%) died in-hospital. During follow-up, 60 (23%) developed non fatal myocardial infarction, 64 (25%) died, 9 (4%) underwent PTCA, 54 (21%) CABG, 179 (70%) were readmitted, 93 (36%) were free of angina. Of the patients who died, 27% died suddenly. In 1988, 283 were admitted. During hospital stay 26 (9%) patients underwent CABG and 43 (15%) PTCA. Myocardial infarction developed in 87 (31%) and 3 (1%) patients died in-hospital. During follow-up non fatal myocardial infarction occurred in 37 (13%) and 42 (15%) patients died ($p<0.05$), 25 (9%) underwent PTCA, 45 (16%) CABG, 158 (56%) were readmitted ($p<.05$), 148 (53%) were free of angina ($p<0.05$). Of the patients who died, 17% died suddenly. Increased age, presence of peripheral vascular disease, a previous history of coronary artery disease and signs of left ventricular dysfunction were related to death during follow-up.

Conclusion: In the eighties patients admitted to hospital because of unstable angina pectoris had a high incidence of usually small myocardial infarctions (approximately 1/3 of the patients) but a low mortality rate (1%). Long-term follow-up revealed a reduction in long-term mortality and morbidity when patient cohorts from 1992 and 1988 are compared. More aggressive acute and chronic reperfusion strategies seem to be responsible for these favorable changes.

INTRODUCTION

Coronary artery disease continues to be the leading cause of mortality and morbidity in many parts of the world. Acute clinical syndromes related to this disease are unstable angina, acute myocardial infarction and sudden cardiac death. Much effort has been spent during the last decades to improve prognosis of these acute coronary syndromes. By performing a meta-analysis we have shown that the in-hospital prognosis of acute myocardial infarction has improved but not prognosis following discharge (1). In a subsequent study we compared the outcome of acute myocardial infarction in patients admitted in the early and late 1980 's and also found an improved in-hospital mortality and morbidity (2). Changes in prognosis of unstable angina pectoris have been less extensively studied. One of the reasons for this may be difficulties in defining this syndrome. In unstable angina new treatment strategies (nitroglycerin (3), Heparin (4), antiplatelets (5), Beta blocking agents (6), calcium-antagonists (7), alone or in combination with invasive strategies such as balloon angioplasty or coronary bypass grafting) have been introduced and their effect on prognosis studied. Before the widespread use of coronary angiography followed by PTCA or coronary bypass grafting the treatment consisted of drug administration to relieve anginal attacks. To study the effect of new treatment modalities on mortality and morbidity of patients admitted with UAP we have compared the patient cohorts with unstable angina admitted in 1982 and 1988. These years were selected because in between these years invasive treatment strategies were introduced in our institution.

METHODS

The clinical records of all patients admitted to the Academic Hospital Maastricht, the Netherlands in 1982 and 1988 with a diagnosis of UAP were reviewed. This hospital is the only hospital in an area with approximately 182,000 inhabitants. The diagnosis of UAP required a history of typical chest pain less than 30 minutes (new onset angina, progression of previously stable angina, angina at rest, persistent angina) and transient electrocardiographic changes during chest pain, normalizing after disappearance of chest pain; ST-segment depression or elevation less than 0.1 mV, or development of negative T-waves. Patients without chest pain on admission were also included in this study when their history was very suggestive of unstable angina. All patients were admitted to the coronary care unit.
When a rise of cardiac enzymes above the upper limit of normal was found in the subsequent evaluation of the patient, the final diagnosis was myocardial infarction. Demographic and clinical variables were collected during admission with emphasis on medical and interventional treatment.

The use of various medications was registered on admission, during hospital stay and during follow-up. All interventions such as thrombolytic therapy, PTCA and CABG were registered.
Follow-up data were obtained from the outpatient chart or from readmissions. If a patient was not followed up at the cardiology outpatient department, a standard questionnaire was sent to the general practitioner to receive information about therapy, complaints or time and cause of death. For every patient there were three fixed time points,
1) admission to hospital; 2) time of death or discharge and 3) the end of 5 years of follow-up.
Only patients were included, living in the area served by the academic hospital of Maastricht, allowing assesment of population based data.

Statistical analysis

The data were analyzed by using the Statistical Package of the Social Sciences (8) and the SAS Statistical program (9). Univariate analysis was performed with Student t-test to compare groups with continuous variables and chi-square for groups with discrete variables. To correct for cells with an expected count less than 5, the likelihood ratio chi-square was used and Fisher's exact test. Variables reaching significance in the univariate analysis together with other relevant variables were used in a stepwise multiple regression analysis to evaluate their independent importance for death during follow-up. Kaplan-Meier curves were constructed to approximate the life expectancy of both patient groups (10). Wilcoxon's test for equality of survival curves was calculated.

RESULTS

Baseline characteristics of the study groups are presented in table 1. No significant differences were found in relation to sex, mean age, percentage of patients with a cardiac enzyme rise, positive family history, incidence of smoking, diabetes or hypertension, incidence of previous myocardial infarction or angina pectoris. The only difference was the incidence of previous CABG (11 (4%) in 1982 vs 32 (11%) in 1988) ($p<0.01$)).
Medical treatment before and during admission was different in both years (Table 2); in 1982, on admission, less patients had aspirin or ACE-inhibitors whereas more patients had diuretics, coumarins or digoxin. At discharge also more patients of 1982 received diuretics, coumarins or digoxin. Beta-blockers, nitrates, Calcium-antagonists, aspirin and ACE-inhibitors were significantly more frequently prescribed in 1988 (Table 2).

Table 1. Baseline variables of all patients with UAP admitted in 1982 and 1988 (percentage within brackets).

	1982 n=258		1988 n =283	
mean age	63.8 SD 9.4		63.6 SD 13.3	
older than 70 years	86	(33)	82	-29
sex (pct male)	150	(58)	178	-63
enzyme rise	79	(31)	87	-31
family history positive	181	(70)	162	-57
smoking	131	(51)	140	-49
diabetes	26	(10)	36	(13)
hypertension	123	(48)	117	(41)
previous CABG *	11	-4	32	-11
previous MI	81	(31)	78	(28)
previous AP	140	(54)	144	(51)

* p<0.01, pct=percentage, CABG=Coronary artery bypass grafting, MI=Myocardial infarction, AP=Angina pectoris

Table 2. Drug treatment on admission and at discharge in 1982 and 1988. (percentages within brackets).

	Admission				Discharge			
	1982 n=258		1988 n=283		1982		1988	
Beta - Blockers	83	(32)	80	(28)	107	(42)	212	(76)**
Nitrates	88	(34)	68	(24)	217	(85)	129	(46)**
Ca - antagonists	31	(12)	40	(14)	84	(33)	126	(45)**
Antiplatelets	5	-2	34	(12)**	3	-1	170	(61)**
Coumarins	31	(12)	17	-6	51	(20)	30	(11) *
Diuretics	88	(34)	51	(18)**	100	(39)	36	(13)**
Ace - inhibitors	0	0	6	(2) *	1	-4	17	(6)**
Digoxin	34	(13)	11	(4)**	56	(22)	14	(5)**

* p<0.05 ** p<0.001

Table 3. Outcome in-hospital and during follow-up of all patients admitted with UAP. (Percentages within brackets).

	1982		1988	
UAP on admission	258		283	
IN-HOSPITAL				
No angina	171	(66)	178	(63)
MI	79	(31)	87	(31)
PTCA ***	1		43	(15)
CABG *	10	(4)	26	(9)
Death	3	(1)	3	(1)
FOLLOW-UP				
No angina ***	93	(36)	148	(53)
Readmission *	179	(70)	158	(56)
Non-fatal MI **	60	(23)	37	(13)
PTCA *	9	(4)	25	(9)
CABG *	54	(21)	45	(16)
Death *	64	(25)	42	(15)

*=p<0.05 **=p<0.01 ***p<0.001; UAP=unstable angina pectoris, PTCA=balloon angioplasty, CABG=coronary artery bypass grafting, MI=myocardial infarction.

Table 4. Causes of death during follow-up of patients admitted with UAP in 1982 and 1988.

	1982		1988	
recurrent MI	17	(27)	9	(21)
sudden death	17	(27)	7	(17)
pump failure *	14	(22)	18	(43)
non cardiac	9	(14)	5	(12)
unknown	7	(11)	3	(7)

MI=Myocardial infarction. * p<0.05

Mortality

As shown in table 3, in-hospital mortality was similar in 1982 and in 1988. All in-hospital deaths in both years had myocardial infarction as final diagnosis. During a follow-up period of 5 years, 64 (25%) patients discharged in 1982 died and 42 (15%) of the 1988 group (p<0.05). Of all patients discharged in 1982, 11 (4.3%) died within the first year. Of the patients discharged in 1988,

13 (4.6%) died within the first year. Fig. 1 shows the survival curves for both years. A significant difference between the cause of death was observed between both cohorts. In 1988 more patients died of pump failure, 14 in 1982 and 18 in 1988. In 1988 less patients died suddenly, 7 versus 17 in 1982 (Table 4).

Morbidity

Also morbidity figures were more favorable in the 1988 than in the 1982 population. A reduction of hospitalization time was observed between both cohorts (1982: 9.8 days, 1988: 8.4 days, p=.05). Readmission rates for cardiac reasons were 70% in the 1982 cohort and 56% in 1988 ($p<0.001$). The reason for readmission was myocardial infarction in 14% and 6% respectively ($p<0.01$), most of the others were admitted because of angina or heart failure. After 5 years the percentages of patients with angina pectoris functional class I according to the criteria of the New York Heart association were 36% (1982) and 53% (1988) ($p<0.001$) respectively.
As shown a significant difference in treatment was observed between both years, patients of 1988 had more drugs (table 2) and were more often treated with either PTCA or CABG (table 3).

Univariate and multivariate analysis

Survivors versus death during follow up

Univariate analysis showed that patients who died during follow-up in both patient cohorts had more frequently a history of peripheral artery disease, cerebrovascular disease and they also experienced more often residual anginal attacks during admission. Five variables related to heart failure were more frequently observed in patients who died of both groups (dyspnea on admission, enlarged heart and signs of congestion on chest X-ray, treatment with diuretics and/or digoxin, Killip class more than 1). Also in both populations the patients who died were older. Other univariate predictors for the 1982 group were: male sex and a high systolic blood pressure. For the 1988 group these were previous myocardial infarction, infarction during admission and a high heart rate. An intervention such as PTCA or CABG was more often performed in patients who survived of the 1988 cohort. However this observation is biased because these patients were younger and also had less frequently a history of previous cardiac disease.
Stepwise multiple regression analysis identified 6 variables independently related to death during 5 years follow-up: peripheral artery disease, admission year 1982, dyspnea, higher age, recurrent angina and a previous cardiac history (Table 5).

Table 5. Variables of prognostic importance for death during follow-up in 1982 and 1988.

	p	sens	spec	ppv	P
peripheral vasc.	<0.001	34	91	50	<.0001
year 1982	<0.01	60	56	26	<.0001
dyspnea	<0.001	24	96	56	<.001
age >70	<0.001	50	77	36	<.001
recurrent angina	0.05	21	76	23	<.05
prev. hist	<0.01	65	51	26	<.05

Figures for sensitivity, specificity, positive predictive value are percentages, p=probability of Chi-square / Student T-test, P=probability > t (multivariate), peripheral vasc= Peripheral vascular disease, prev. hist=previous cardiac history, year 1982=admitted in 1982

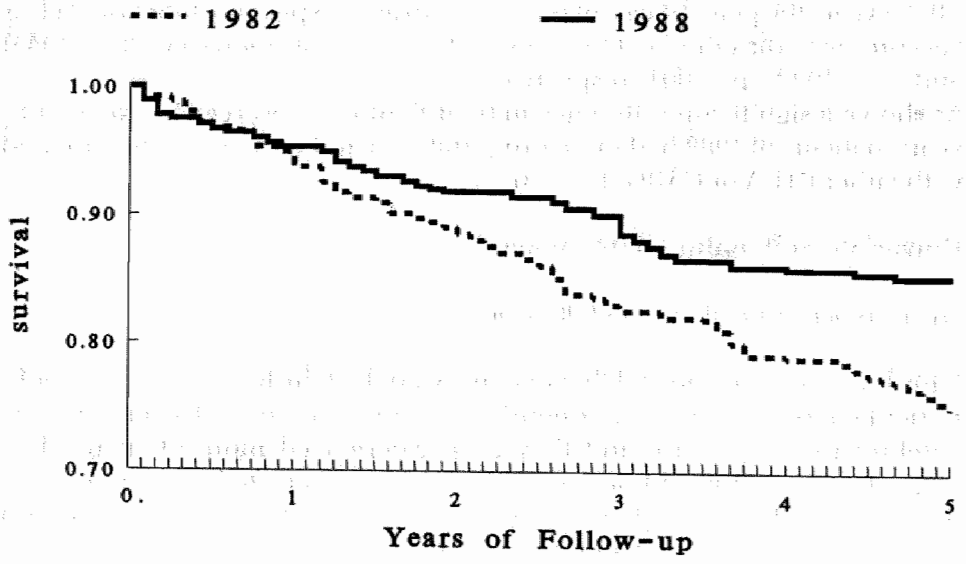

Figure 1. Survival curves of patients admitted with unstable angina pectoris in 1982 and 1988. Wilcoxon's test for equality of survival curves; Chi-square 3.9329, p<0.05

DISCUSSION

Unstable angina pectoris is caused by either increased myocardial oxygen demand in the presence of severely restricted coronary reserve or by a dynamic narrowing caused by thrombosis or coronary vasoconstriction or both (11).

Patients with UAP have an increased risk for sudden death, or acute myocardial infarction (12-14). The clinical presentation may be one of new onset angina, progressive angina, angina at rest, or persistent angina. The challenge of unstable angina is to individualize the treatment and to identify high risk patients requiring more aggressive strategies (15-17). Because new treatment modalities have become available in the 1980's, we were interested to study whether this has resulted in an improved outcome in patients with MI and UAP (2). Thrombolytic therapy, PTCA and CABG are the clearest examples of new approaches to patients with acute coronary syndromes. Randomized placebo controlled trials have proven the benefit of thrombolytic therapy and PTCA in acute MI patients. In unstable angina the benefit of these interventions have been less clear (32), moreover the results have been obtained in selected patient groups. In daily practice only a subset of patients actually receives this treatment. Prognosis has been improved by drugs such as heparin and aspirin; this has resulted in differences in medication prescribed in our patient cohorts of 1982 and 1988 (table 2). Numerous studies have shown the benefits of these new treatments versus the conventional ones (18-32). This study suggests that the use of these new interventions has also improved the prognosis in a more general patient group.

To avoid selection, no patients were included, referred from other institutions. Because the Academic Hospital of Maastricht is the only community hospital serving a well defined area of nearly 180.000 inhabitants, the patient cohorts are representative for the whole Dutch population. Apart from a higher incidence of previous CABG, no differences in baseline characteristics were found between 1982 and 1988. There were no exclusions in relation to age, previous infarctions, treatment etc. The aim was to include the whole spectrum of unstable angina pectoris patients. Patients admitted with symptoms and electrocardiographic changes typical for unstable angina will have two different diagnosis at discharge, unstable angina and myocardial infarction. The 1982 patients were mainly treated medically with oral drugs whereas in 1988, PTCA and CABG were frequently performed when indicated, after stabilization of the patient was attempted with intravenously administered nitroglycerine and heparin. In the literature myocardial infarction rates in patients admitted with a diagnosis of unstable angina vary from 10% to 30% (32). We also found a high incidence of myocardial infarction especially because we classified patients as MI if their enzymes exceeded the normal value instead of a two or threefold rise as was

done in other studies. It is therefore of importance to notice that a subgroup of patients with myocardial infarction is not identified as such on admission and probably therefore less than optimally treated.
Of the 1982 group, 30.6% developed myocardial infarction proven by serial enzyme changes. In 1988 this was 30.7%, most of the infarctions were small (almost 50% in both years had a maximum SGOT rise less than 2.5 times the upper limit of normal). The in-hospital mortality we found is low and comparable to other studies (1-6%)(14,20,33-36).
The comparison of our data with those of others is of limited value because of the different inclusion criteria and the different follow up periods. Also the different definitions of UAP lead to a divergence in prognostic data (30,31). Braunwald made an attempt to correct this problem and developed a classification which has been validated recently and it became clear that subgroups of patients can be defined with low, intermediate and high risk (37,38). Inclusion in our study started before these criteria were available and for reasons of comparability of the different years we continued the study with the initial inclusion criteria. Most of our patients would have been included in Braunwald group 3 because of the fact that they had complaints within the 48 hours before admission. The reported first-year mortality averages from 5.5 to 14 % in different studies and averages from 3.4 to 6% per year thereafter, in one study an annual mortality of 2 % was observed (19). We found an annual mortality of 5% for patients admitted in 1982 and 3% for those admitted in 1988. First year mortality was almost the same for both cohorts whereas a significant lower mortality was observed between 1 and 5 years, so it appears that after one year the reduction in mortality becomes clear. This finding underlines the importance to perform studies with a long follow-up time. Of importance are our findings concerning morbidity. Of the patients treated in 1988 significantly more were in functional class I and less readmissions were observed which may be relevant for the discussion about costs of treatment due to the use of new therapies.
Although almost 30% of the 1988 patients were over the age of 70 we found a low mortality in this older age group. The intervention rate in 1988 was high, 114 patients were catheterized of whom 43 underwent PTCA and 27 CABG. Of these 114 patients, 1 died in-hospital. However these more aggressively treated patients were younger (mean age 1982: 57.9 years, mean age 1988: 61.1 years) and had a slightly lower incidence of previous angina (1982: 48%, 1988: 45%) and previous myocardial infarction (1982: 31%, 1988: 22%).
It has been shown by different investigators that increased age, angina in rest after hospital admission, a history of angina or previous myocardial infarction and signs of left ventricular dysfunction are variables related to an adverse prognosis in patients with UAP (14,20,24,36,39). The outcome in our patients supports these findings. An important univariate predictor for a beneficial outcome for the 1988 patients was the advent of PTCA or CABG.

In this patient group a low mortality and morbidity was observed. In the multivariate analysis this variable did not show to be of significance because of its relation with age.
A possible limitation of this study is its retrospective design so that accurate quantification of some variables and cardiac risk factors was not possible.

REFERENCES

1. Vreede De JJM, Gorgels APM, Verstraaten GMP, Vermeer F, Dassen WRM, Wellens HJJ. Did prognosis after myocardial infarction change during the past 30 years? A meta analysis. J Am Coll Cardiol 1991;18:698-706.
2. Widdershoven JWMG, Gorgels APM, Verstraaten GMP, Vermeer F, Wellens HJJ. Decline in in-hospital mortality after acute myocardial infarction between 1982 and 1988. Neth J Cardiol 1991;4:255 (abstract).
3. Curfman GD, Heinsimer JA, Lozner EC, Fung H. Intravenous nitroglycerin in the treatment of spontaneous angina pectoris: a prospective, randomized trial. Circulation 1983;67:276-82.
4. Williams DO, Kirby MG, McPherson K, Phear DN. Anticoagulant treatment in unstable angina. Br J Clin Pract 1986;40:114-7.
5. Lewis HD, David JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE, Schnaper HW, LeWinter MM, Linares E, Pouget JM, Sabharwal SC, Chesler E , DeMots H. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. N Engl J Med 1983;309:396-9.
6. Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) Research Group: Early treatment of unstable angina in the coronary care unit: a randomized, double-blind, placebo-controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both. Br Heart J 1986;56:400-4.
7. Mehta j, Pepine CJ, Day M, Guerrero JR, Conti CR. Short-term efficacy of oral verapamil in rest angina. A double-blind placebo-controlled trial in CCU patients. Am J Med 1981;71:977-82.
8. Norusis MJ. Base manual. SPSS Inc. Chicago, Illinois (USA) 1988.
9. SAS/STAT User's guide, version 6, fourth edition, vol I, Cary,NC:SAS Institute Inc;1989:943.
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
11. Maseri A. Pathogenetic classifications of unstable angina as a guideline to individual patient management and prognosis. Am J Med 1986;80(suppl 4c):48-55.
12. Falk E. Unstable angina with fatal outcome: Dynamic coronary thrombosis leading to infarction and/or sudden death. Circulation 1985;71:699-708.
13. Fischl SJ, Herman MV, Gorlin R. The intermediate coronary syndrome: clinical, angiographic and therapeutic aspects. N Engl J Med 1973:288;1193-7
14. Krauss KR, Hutter AM, De Sanctis RW. Acute coronary insufficiency; course and follow-up. Circulation 1972;45/46:suppl I:66-70.
15. Moss AJ. Profile of high risk in people known to have coronary heart disease; a review. Circulation 1975;52:suppl III:147-53.
16. Vlietstra RE, Assad Morell JL, Frye RLK, Elveback LR, Conolly DC, Ritman EL, Pluth JR, Barnhorst DA, Danielson GK, Wallace RB. Survival predictors in coronary artery disease: medical and surgical comparisons. Mayo Clin Proc 1977;52:85.

17. Ouyang P, Brinker JA, Mellits ED, Weisfeldt ML, Gerstenblith G. Variables predictive of successful medical therapy in patients with unstable angina: selection by multivariate analysis from clinical, electrocardiographic, and angiographic evaluations. Circulation 1984;70:367-76.
18. De Servi S, Berzuini C, Poma E, Ghio S, Scire A, Cioffi P, Ardissino D, Montemartini C, Specchia G. Long-term survival and risk stratification in patients with angina at rest undergoing medical treatment. Int J Cardiol 1989;22:43-50.
19. Severi S, Michelassi C, Orsini E, Marraccini P, L'Abbate A. Long-term prognosis of transient acute myocardial ischemia at rest. Am J Cardiol 1989;64:889-95.
20. Gazes P, Mobley EM, Faris HM, Duncan RC, Humphries GB. Preinfarctional (unstable) angina-a prospective study-ten year follow-up: prognostic significance of electrocardiographic changes. Circulation 1973;48:331-7.
21. Lewis HD, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE III, Schnaper HW, Lewinter MM, Linares E, Pouget JM, Sabharwal SC, Chesler E, DeMots H. Prospective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of Veterans Administration Cooperative Study. N Engl J Med 1983;309:396-403.
22. Graham I, Mulcahy R, Hickey N, O'Neill W, Daly L. Natural history of coronary heart disease: a study of 586 men surviving an initial acute attack. Am Heart J 1983;105:249-57.
23. Harris PJ, Lee KL, Harrel FE, Behar VS, Rosati RA. Outcome in medically treated coronary artery disease. Ischemic events: nonfatal infarction and death. Circulation 1980;62:718-26.
24. De Servi S, Berzuini C, Ghio S, Ferrario M, Poma E, Scire A, Ragni T, Vigano M, Montemartini C, Specchia G. Effects of surgical versus medical treatment on long-term prognosis in angina at rest: an observational non-randomized study of 400 patients. Eur Heart J 1988;9:513-19.
25. Hultgren HN, Pfeifer JF, Angell WW, Lipton MJ, Bilisoly J. Unstable angina: comparison of medical and surgical management. Am J Cardiol 1977;39:734-40.
26. Parisi AF, Khuri S, Deupree RH, Sharma GVRK, Scott SM, Luchi RJ. Medical compared with surgical management of unstable angina: 5-year mortality and morbidity in the veterans administration study. Circulation 1989;80:1176-88.
morbidity in the veterans administration study. Circulation 1989;80:1176-88.
27. Unstable Angina Pectoris Study Group. Unstable angina pectoris: National Cooperative Study Group to Compare Surgical and Medical Therapy. I. Report of protocol and patient population. Am J Cardiol 1976;37:896-902.
28. Unstable Angina Pectoris Study Group. Unstable Angina Pectoris: National Cooperative Study Group to Compare Surgical and Medical Therapy. II. In-hospital experience and initial follow-up results in patients with one, two and three vessel disease. Am J Cardiol 1978;42:839-48.
29. Luchi RJ, Scott SM, Deupree RH, and the Principal Investigators and Their Associates of Veterans Administration Cooperative Study No. 28. Comparison of medical and surgical treatment for unstable angina pectoris. Results of a Veterans Administration Cooperative Study. N Engl J Med 1987;316:977-84.
30. De Feyter PJ, Serruys PW, vd Brand M, Hugenholtz PG. Percutaneous transluminal angioplasty for unstable angina. Am J Cardiol 1991;68:125B-35B.
31. De Feyter PJ, Suryapranata H, Serruys PW, Beat K, van Domburg R, vd Brand M, Tijssen JJ, Azar AJ, Hugenholtz PG. Coronary angioplasty for unstable angina: Immediate and late results in 200 consecutive patients with identification of risk factors for unfavorable early and late outcome. J Am Coll Cardiol 1988;12:324-33.

32. Bär FW, Verheugt FW, Col J, Materne P, Monnasier JP, Geslin PG, Metzger J, Raynaud P, Foucault J, de Zwaan C, Vermeer F. Thrombolysis in patients with unstable angina improves the angiographic but not the clinical outcome. Results of UNASEM, a multicenter, randomized, placebo-controlled, clinical trial with anistreplase. Circulation 1992;86:131-7.
33. van Miltenburg-van Zijl AJM. Management policies and prognosis in unstable angina pectoris. Thesis Rotterdam (The Netherlands) 1992.
34. Cairns JA, Singer J, Gent M et al. One year mortality outcomes of all coronary and intensive care unit patients with acute myocardial infarction, unstable angina or other chest pain in Hamilton, Ontario, a city of 375,000 people. Can J Cardiol 1989;5:239-46.
35. Theroux P, Ouimet H, McCans J et al. Aspirin, Heparin, or both to treat acute unstable angina. N Engl J Med 1988;319:1105-11.
36. Heng MK, Norris RM, Singh BN, Partridge JB. Prognosis in unstable angina. Br Heart J 1976;38:921-5.
37. Braunwald E. Unstable angina. A classification. Circulation 1989;80:410-4.
38. van Miltenburg-van Zijl AJM, Simoons ML, Veerhoek RJ, Bossuyt PMM. Incidence and follow-up of Braunwald subgroups in unstable angina pectoris. J Am Coll Cardiol 1995;25:1286-92.
39. Olson HG, Lyons KP, Aronow WS, Stinson PJ, Kuperus J, Waters HJ. The high risk angina patient; identification by clinical features, hospital course, electrocardiography and technetium-99m stannous pyrophosphate scintigraphy. Circulation 1981;64:674-84.

CHAPTER 7

Acute Myocardial Infarction 'Disguised' as Unstable Angina Pectoris:

Incidence, Clinical and Prognostic Aspects

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ABSTRACT

On admission to the hospital patients are identified as having acute myocardial infarction (MI) on the basis of the medical history and characteristic ECG changes. That diagnosis will result in treatment directed to prevent further loss of myocardium. However some patients will present with chest pain and ECG findings not fulfilling "classical" MI criteria. In that subgroup of patients serial enzyme changes may allow the diagnosis of MI.

To assess the incidence and 1 year prognosis of the group in whom the admission diagnosis changed from unstable angina (UAP) to MI in comparison to the group in whom the diagnosis remained unstable angina, the infarct population and the unstable angina population admitted in 1982, 1988 and 1994 were compared.

In the three observation years 805 patients were admitted as UAP of whom 137 (17%) showed a cardiac enzyme rise, typical for acute MI. (group A); 38 in 1982, 40 in 1988 and 59 in 1994. The diagnosis remained UAP in 668 patients (group B); 220 in 1982, 243 in 1988 and 205 in 1994.

Of group A patients, 1 (1%) died in-hospital and 11 (8%) during a follow-up of 1 year. Signs of heart failure during admission were observed in 13%. Sixty-three percent were free of angina at discharge. Of those who were discharged, 60% were readmitted, 4% had recurrent infarction and 49% were free of angina after one year. Of the patients of group B, 7 (1%) died in-hospital and 37 (6%) during 1 year follow-up. Signs of heart failure during admission were observed in 5% ($p<.05$) and 82% were free of angina at discharge ($p<.05$). Following discharge, 48% were readmitted ($p<.05$), 5% had recurrent infarction and 63% had no anginal complaints after one year ($p<.05$). The predominant abnormality on the electrocardiogram of group A patients was ST-segment depression (49%), ST-segment elevation (26%), changing polarity of T-waves (14%), miscellaneous changes (11%). Of the patients of group A, 14 (10%) had enzymatically an extensive infarction (ASAT >250 U/L) of whom 10 (71%) showed ST-segment depression. Variables independently related to the final diagnosis MI were dyspnea on admission (Relative Risk 3.39 95%CI 2.04-7.11), absence of hypertension (Relative Risk 2.84 95%CI 2.11-3.90) and no previous angina (Relative Risk 3.01 95%CI 1.95-5.5).

It is concluded that mortality of patients not recognized as MI on admission equals mortality of patients in whom the diagnosis remains UAP. However they more frequently have signs of heart failure and residual angina, require more readmissions and have more often anginal complaints during follow-up.

INTRODUCTION

Both unstable angina pectoris and acute myocardial infarction are acute coronary syndromes, however with different therapeutic approaches. Whereas thrombolytic therapy is the treatment of choice in acute MI, it is of questionable value in patients with unstable angina (1). Correct classification is important to have patients benefit optimally from presently available treatment strategies.

Not every patient with acute myocardial infarction fulfills the classical ECG criteria on admission to hospital. This leads to an admission diagnosis of unstable angina pectoris or impending myocardial infarction in approximately 30% of patients (2-4). The current policy is to admit and treat these patients on a coronary care unit with heparin and i.v. nitroglycerin and to await serial cardiac enzyme levels. A rise will lead to a final diagnosis of myocardial infarction and further treatment will be directed towards prevention of residual angina.

However if these patients would have been recognized as MI during admission treatment would have been directed towards reperfusion of the ischemic area.

METHODS

The incidence of myocardial infarction in patients admitted with unstable angina was assessed and differences were studied between the group in whom the admission diagnosis changed from UAP to MI (group A) and in whom it remained UAP (group B). The clinical and 1-year follow up data of all patients admitted in 1982, 1988 and 1994 with unstable angina were reviewed with special attention to treatment, mortality and morbidity.

The diagnosis was based on a history of less than 30 minutes of chest pain (recent onset angina at minimal exertion or at rest, progression of previously stable angina, accompanied by serial ST-segment changes. ST-segment elevation less than 0.1 mv in the extremity leads or the precordial leads, changing polarity of the T-waves, appearance of negative T-waves more than or equal to 0.1 mV or ST-segment depression more than or equal to 0.1 mV accompanied by chest pain). Patients were included in this analysis if a rise in aspartate aminotransferase (SGOT) above the upper limit of normal (40 U/l) could be demonstrated and the subsequent release pattern of SGOT was typical for acute myocardial infarction. The elevation of SGOT was required within 24 hours after admission.

Excluded were patients after prolonged resuscitation or patients who died within one hour after admission before any treatment was started. Also patients without a normal SGOT on admission (subacute myocardial infarction) were excluded. Data were collected from the clinical records and

from follow-up visits at the outpatient clinic. If a patient was lost during follow-up, the general practitioner was interviewed to obtain information about treatment, complaints or time and cause of death. We assessed all readmissions, reinfarctions and the functional class of angina pectoris and dyspnea during a follow-up of one year. Only a small number of patients of the study years 1982 and 1988 was catheterized when indicated according to the opinion of the attending physician or if required according to a study-protocol. Of these patients the coronary angiograms were reviewed to assess the culprit vessel.
According to the dominant findings on the electrocardiogram, patients were classified in different subgroups: ST segment depression, ST segment elevation, changing polarity of T waves, miscellaneous changes.

Statistical analysis

The data were analyzed using the Statistical Package of the Social Sciences (5) and the SAS program (6).
Bivariate analysis was performed with Student t-test to compare groups with continuous variables and Chi-square for groups with discrete variables. To correct for cells with an expected count less than 5, the likelihood ratio Chi-square was used and Fisher's exact test. Variables reaching significance in the bivariate analysis together with other relevant variables were used in a multiple regression analysis. The independent importance of different variables was calculated for the final diagnosis of unstable angina pectoris or myocardial infarction.
Data are presented as mean $\pm$ standard deviation.

RESULTS

In the three observation years 805 patients were admitted with UAP of whom 137 (17%) showed a cardiac enzyme rise, typical for acute MI. (group A); 38 in 1982, 40 in 1988 and 59 in 1994. The diagnosis remained UAP in 668 patients (group B); 220 in 1982, 243 in 1988 and 205 in 1994.
Baseline characteristics of both groups are shown in table 1.
More patients in group A were male, they had less frequently hypertension and a history of anginal complaints and more often dyspnea on admission (Table 1). There was no difference in the duration of previous angina in both groups.

Table 1. Baseline characteristics of patients admitted with UAP in whom the diagnosis remained UAP (group A) (n=137) and in whom it changed from UAP to MI (group B) (n=668).

	group A n=137	%	group B n=668	%
age mean ± sd	63.9 ± 12.1		62.1 ± 10.4	
male gender*	98	72	382	57
fam hist positive	79	58	389	58
diabetes	15	11	82	12
hypertension*	18	13	291	44
smoking	71	52	293	44
previous angina*	50	36	330	49
previous MI	38	28	197	29
previous PTCA	6	4	40	6
previous CABG	14	10	72	11
previous CVA	6	4	43	6
claudication	18	13	60	9
dyspnea on admission*	22	16	52	8

*=$p<0.05$, sd=standard deviation, fam hist pos=positive family history of coronary heart disease, MI=myocardial infarction, PTCA=balloon angioplasty, CABG=coronary arterial bypass grafting, CVA=cerebro vascular accident.

The predominant abnormality on the electrocardiogram of the patients of group A was ST-segment depression (49%), ST-segment elevation (26%), changing polarity of T-waves (14%), miscellaneous changes (11%). Of patients from group A, 46% had a small infarction (SGOT < 100 U/L), 33% showed an SGOT between 100 and 200 U/L and 21% above 200U/L. An extensive infarction with an SGOT above 250 U/L) was observed in 10% with 71% showing ST-segment depression.

Of the patients of group A, 2% were treated with thrombolytics, 12% received PTCA and 7% CABG. For group B these figures were 4%, 14% and 11% (Table 2). None of the patients of group A had a reinfarction during admission. Of the patients of group B, 3% showed an infarction during hospital stay.

Hospital mortality was 1% (1 patient of group A and 7 patients of group B). During a follow up of one year, 48 (6%) patients died (8% of group A and 6% of group B).

Drug treatment was different in both groups; less patients of group A were using calcium-antagonists on admission. At discharge, more patients of group A were using ACE-inhibitors, digoxin and nitrates (Table 3 and 4).

Table 2. Interventions, in-hospital outcome and outcome during follow-up of patients with final diagnosis MI (group A) or UAP (group B).

	group A n=137	%	group B n=668	%
IN-HOSPITAL				
Thrombolytics	3	2	29	4
PTCA	16	12	94	14
CABG	9	7	72	11
(Re)-infarction	0	0	19	3
Heart failure*	18	13	36	5
No angina at discharge*	86	63	548	82
Death	1	1	7	1
FOLLOW-UP	n=136		n=661	
Readmission cardiology*	82	60	318	48
(Re)-infarction	6	4	35	5
PTCA	6	4	39	6
CABG	14	10	50	7
No angina, 1 year*	67	49	416	63
Death	11	8	37	6

*p<0.05, PTCA=Balloon angioplasty, CABG=coronary arterial bypass grafting.

Table 3. Drug treatment on admission in group A and group B.

	group A n=137	%	group B n=668	%
Beta blocker	46	34	235	35
Nitrates	42	31	254	38
Aspirin	24	18	145	22
Calcium ant.*	20	15	169	25
Diuretics	35	26	185	28
Coumarins	18	13	73	11
Ace inhibitors	9	7	43	6
Digoxin	13	9	48	7

*p<0.05

Because patients admitted in 1994 were more often catheterized than those admitted in previous years, a subanalysis was performed in the 1994 patient group. In patients of group A who were catheterized (36%), no differences were found as to the culprit vessel of the three coronary arteries. However, 61% showed three vessel disease (Table 5).

Table 4. Drugs at discharge in group A and group B.

	group A n=137	%	group B n=668	%
Beta blockers	85	62	442	66
Nitrates*	116	85	373	56
Aspirin	72	53	342	51
Calcium ant	56	41	315	47
Diuretics	38	28	171	26
Coumarins	28	20	128	19
ACE inhibitors *	20	15	58	9
Digoxin *	24	18	71	11

*=p<0.05

Table 5. Number of diseased vessels and culprit lesion in patients of group A, admitted in 1994 (n=49).

Number of diseased vessels		Culprit lesion	
1	13%	LAD	33%
2	26%	RCX	39%
3	61%	RCA	28%

Morbidity

Table 2 shows that patients of group B showed less often signs of heart failure during admission and were also more often free of angina pectoris at discharge.

After a follow-up of one year, 82 (60%) of the patients of group A were at least once readmitted for cardiac reasons. A non-fatal reinfarction occurred in 6 (4%). PTCA was done in 6 (4%) patients and 14 (10%) were operated. After one year 125 (91%) of the patients of group A were still alive of whom 49% had no anginal complaints according to the criteria of the New York heart association.

Of the patients discharged of group B, 318 (48%) were readmitted at least once (p<.05). Infarction occurred in 35 (5%) patients. PTCA was performed in 39 (6%) patients during follow-up and 50 (7%) patients were operated. After one year 624 (93%) patients were still alive of whom 63% (p<.05) were free of angina. (table 2).

Bivariate analysis and multiple regression

With bivariate analysis 4 variables were identified related to the final diagnosis of myocardial infarction: male gender, absence of hypertension on admission, no previous anginal complaints and dyspnea on admission. These variables together with other relevant variables were entered in a multiple logistic regression model. With this model three variables were identified as independently related to the final diagnosis of myocardial infarction; the absence of hypertension on admission (Relative Risk 2.84 95%CI 2.11-3.90), no previous anginal complaints (Relative Risk 3.01 95%CI 1.95-5.5) and complaints of dyspnea (Relative Risk 3.39 95%CI 2.04-7.11).

DISCUSSION

Unexpected MI frequently occurs in patients admitted with the diagnosis of unstable angina pectoris. Apparently myocardial tissue loss may occur in electrocardiographically silent areas; the typical example being the area supplied by the circumflex coronary artery.
Because Q-waves as marker for transmural infarction were absent (7-9), we used the cardiac enzymes to diagnose the presence or absence of infarction. The main finding of this study is that mortality (in-hospital or during a follow-up of one year) of unselected patients admitted with a diagnosis of UAP followed by a subsequent rise in cardiac enzymes is low and equals mortality of patients in whom the diagnosis remains UAP. There were differences in baseline characteristics between both groups. More patients with MI had complaints of dyspnea on admission suggesting a diminished left ventricular function due to muscle loss or more extensive ischemia. More patients with UAP had a history of previous anginal complaints possibly related to the formation of protective collaterals (10) and more patients with UAP were on calcium-antagonists on admission to hospital. More patients of group A had complaints related to heart failure during admission which is also reflected in the drug regimen at discharge. They received more often nitrates, ACE-inhibitors and digoxin.
During follow-up patients with MI were more frequently readmitted. Despite equal mortality, there was a difference in incidence of heart failure during admission and on readmission underlining the importance of making an early diagnosis of MI on admission to the hospital. Our observations indicate that in patients presenting with ischemic chest pain, there is still a patient group in whom the final diagnosis is uncertain until the cardiac enzymes are known (11-14). In this group an echo is helpful to assess regional wall motion abnormalities and if extensive ischemia can be demonstrated cardiac catheterization with, when necessary, an attempt to reperfusion should be considered. Also cardiac troponin T in serum appears to be a sensitive

indicator of myocardial cell injury (15). The admission electrocardiogram could not predict the subgroup of patients with larger infarction.
ST-segment depression, elevation and changes in polarity of T-waves were equally divided between the groups.
It is concluded that 17% of patients admitted to hospital under the diagnosis unstable angina have enzyme changes diagnostic for acute myocardial infarction. Only a minority (10%) of these patients have a sizable infarction. It is of importance however to diagnose acute MI in patients admitted with UAP because of a higher incidence of heart failure complaints, readmissions and higher functional class of angina pectoris.

REFERENCES

1. Bär FW, Verheugt FW, Col J, Materne P, Monnasier JP, Geslin PG, Metzger J, Raynaud P, Foucault J, de Zwaan C, Vermeer F. Thrombolysis in patients with unstable angina improves the angiographic but not the clinical outcome. Results of UNASEM, a multicenter, randomized, placebo-controlled, clinical trial with anistreplase. Circulation 1992;86:131-7.
2. Yusuf S, Pearson M, Sterry H, Parish S, Ramsdale D, Rossi P, Sleight P. The entry ECG in the early diagnosis and prognostic stratification of patients with suspected acute myocardial infarction. Eur J Cardiol 1984;5:690-6.
3. Schroeder JS, Lamb IH, Harrison DC. Patients admitted to the coronary care unit for chest pain: high risk subgroup for subsequent cardiovascular death. Am J Cardiol 1977;39:829-32.
4. Karlson BW, Herlitz J, Wiklund O, Richter A, Hjalmarson A. Early prediction of acute myocardial infarction from clinical history, examination and electrocardiogram in the emergency room. Am J Cardiol 1991;68:171-5.
5. Norusis MJ. Base Manual. SPSS Inc. Chicago, Illinois (USA) 1988.
6. SAS/STAT User's guide, version 6, fourth edition, vol 1. Cary,NC:SAS Institute Inc;1989:943.
7. Phibbs B. 'Transmural' versus 'subendocardial' myocardial infarction: an electrocardiographic myth. J Am Coll Cardiol. 1983;1:561-4.
8. Spodick DH. Q-wave infarction versus S-T infarction: nonspecificity of electrocardiographic criteria for differentiating transmural and nontransmural lesions. Am J Cardiol. 1983;51:913-5.
9. Klein LW, Helfant RH. The Q-wave and non-Q wave myocardial infarction: differences and similarities. Prog Cardiovasc Dis. 1986;29:205-20.
10. Kloner RA, Shook T, Przyklenk K, Davis VG, Junio L, Matthews RV, Burstein S, Gibson M, Poole WK, Cannon CP. Previous angina alters in-hospital outcome in TIMI 4. A clinical correlate to preconditioning? Circulation 1995;91:37-45.
11. Goldman L, Weinberg M, Weisberg M, Olshen R, Cook EF, Sargent RK, Lamas GA, Dennis C, Wilson C, Deckelbaum L, Finberg H, Striratelli R, and the medical house staff at Yale-New Haven hospital and Brigham and Women's hospital. A computer-derived protocol for the aid in the diagnosis of emergency room patients with acute chest pain. N Engl J Med 1982;307:588-96.
12. Morris AL, Reimer J. Suspect myocardial infarction: hospital management and prognosis. Clin Cardiol 1983;6:285-91.

13. Tierney WM, Fitzgerald J, McHenry R, Roth BJ, Psaty B, Stump DL, Anderson K. Physician's estimates of the probability of myocardial infarction in emergency room patients with chest pain. Med Decis Making 1986;6:12-17.
14. Fesmire FM, Percy RF, Wears RL, MacMath TL. Risk stratification according to the initial electrocardiogram in patients with suspected acute myocardial infarction. Arch Intern Med. 1989;149:1294-7.
15. Gokhan-Cin V, Gok H, Kaptanoglu B. The prognostic value of serum troponin T in unstable angina. Int J Cardiol 1996;53:237-44.

PART II

Sudden Cardiac Arrest

CHAPTER 8

Out-of-Hospital Cardiac Arrest in the 1990s

A Population Based Study in the Maastricht Area on Incidence, Characteristics and Survival

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ABSTRACT

Incidence and survival rates of out-of-hospital sudden cardiac arrest in different communities are often based on the number of victims resuscitated by the emergency medical services. Our population based study in the Maastricht area included witnessed and unwitnessed sudden cardiac arrest victims outside hospital.

Incidence, characteristics of patients and survival rates were determined by prospectively collecting information from all cases of sudden cardiac arrest occurring in the age group 20 to 75 years between January 1, 1991 and December 31, 1994. Survival rates were related to the site of the event (home versus outside home), the presence or absence of a witness and the rhythm at the time of the resuscitation attempt in out-of-hospital sudden cardiac arrest.

515 cases were included (72% men and 28% women). In 44% of men and 53% of women sudden cardiac arrest was most likely the first manifestation of heart disease. In patients known with a previous myocardial infarction the mean time interval between myocardial infarction and sudden cardiac arrest was 6.5 years with more than half of them having a left ventricular ejection fraction of more than 30%. Mean yearly incidence of sudden cardiac arrest was 1/1000 inhabitants. Of all deaths in the age groups studied 18.5% were sudden. Nearly 80% of sudden cardiac arrest occurred at home. In 60% of all sudden cardiac arrest cases a witness was present. Cardiac resuscitation, which was attempted in 51% of all cases, resulted overall in 32/515 (6%) patients discharged alive from hospital. Survival rates for witnessed sudden cardiac arrest were 16/208 (8%) at home and 15/85 (18%) outside (95% CI 2% - 18%).

The majority of sudden cardiac arrest victims cannot be identified before the event. Sudden cardiac arrest usually occurs at home and survival of witnessed sudden cardiac arrest at home was low compared to outside, indicating the necessity of optimizing out-of-hospital resuscitation especially in the at home situation.

INTRODUCTION

In the industrialized countries many people die from sudden cardiac arrest (SCA) with coronary heart disease as the most common cause (1).
To develop and evaluate preventive strategies such as selecting target groups for cardiopulmonary resuscitation (CPR) training, it is important to know the yearly incidence of SCA in the community, the circumstances surrounding SCA, the patient profile and the factors determining survival. Incidence rates of SCA range from 36 to 128 per 100,000 inhabitants per year in different communities (2-5). However, in these studies only witnessed cardiac arrest victims seen or resuscitated by the emergency medical services (EMS) were included. Furthermore, as pointed out by Siscovick (6) and Becker (2), true incidence information has been a neglected factor in evaluating survival rates.
In our study region there is only one hospital, one EMS and a network of cooperative general practitioners (GP) what makes the region suitable for population based studies. In this article we report on the yearly incidence during a four year period of unexpected witnessed and unwitnessed cases of SCA in the Maastricht area in the Netherlands. Furthermore we report on the medical characteristics of the victims and on the relation between survival and site of SCA.

METHODS

Study population

During a four year period (January 1st, 1991-December 31 st, 1994) all victims of unexpected out-of-hospital SCA between the ages of 20 and 75 years and living in the region of Maastricht in the Netherlands were registered. The area encloses 203 square kilometers and has approximately 182,000 inhabitants of whom around 133,000 (73%) are between the ages of 20 and 75 years. In this area there is only one EMS which has seven ambulances. All seven ambulances are equipped with defibrillators, material for intubation and oxygen administration and medication like adrenaline, atropine, lidocaine and procainamide. The ambulance service can be contacted 24 hours a day by calling 112. Each ambulance has one nurse and one driver. In case of SCA, always two ambulances are immediately directed to the scene.

Inclusion and exclusion criteria

Included in this study were all witnessed and unwitnessed victims of SCA living in the study region. Unwitnessed cases were included when

circumstances were pointing to an unexpected SCA (for example those who died unexpectedly during sleep). Excluded were patients with a circulatory arrest following a traumatic event or intoxication or SCA occurring in the terminal phase of a chronic disease.
The age limit of 75 years was chosen because inhabitants who are above this age are often living alone, limiting the possibility to obtain information about circumstances of death and complaints preceding the event.

Data collection

All victims who were found dead and/or in whom no ambulance was present were reported by the general practitioners in the region. All victims in whom an ambulance was involved were reported by the ambulance personnel. The ambulance service was contacted daily. All 84 general practitioners located in the study region were phoned weekly.
In all cases information was collected about age, gender, circumstances and whether and by whom the SCA was witnessed. This information was obtained from the ambulance personnel, the general practitioner and/or family members or witnesses who were interviewed later. Information about: performance of CPR and by whom, the cardiac rhythm at the moment of arrival of the ambulance, the estimated time interval between the moment of collapse and the start of the resuscitation and the ambulance delay time (time between the moment of the emergency call and the moment of arrival) were obtained from a questionnaire which was filled out immediately after the event by the ambulance personnel.
Information about the medical history of victims was gathered by collecting information from the GPs and by examining the medical hospital records.
Data about the overall mortality in our study population was obtained from the Central Statistical Office. These data will be presented according to gender and age (age range 25 to 75 years).

Definitions

Incidence of SCA

Yearly incidence of SCA was assessed for 1991, 1992, 1993 and 1994 separately by dividing the total number of cases registered each year by the total number of inhabitants in the same age-range standardized for 10,000 inhabitants.
Data on the total number of residents in the region (calculated on January 1st of each year), and information about gender and age distribution of the population in the region were obtained from the Central Statistical Office (7).
The mean yearly incidence of SCA over the total study period for inhabitants with and without known cardiac disease were also estimated. Incidence rates

were calculated similarly as above. Prevalence of cardiac disease in the community was estimated by using information from the regional registration network of general practitioners (8). This network consists of 42 participating general practitioners in 15 practices of the district of Limburg. The patient population of the network resembles the general population of the Netherlands with respect to age, sex, marital status, type household, insurance status and level of education (8). The data-base contains information about the medical history of a representative group of 12,061 inhabitants of the Maastricht area in Limburg. Age and gender adjusted prevalence of cardiac disease in this sample was extrapolated to the study population.
The presence of a cardiac disease was defined as known with angina pectoris, myocardial infarction, heart failure, valvular disease, arrhythmias or other heart diseases.

Sudden Cardiac Arrest

Sudden cardiac arrest was defined as unexpected, non traumatic loss of vital signs, such as consciousness, arterial pulse, blood pressure and respiration without preceding complaints or within 24 hours of the onset of complaints. We used the 24 hours definition to include also those victims who were found dead, but who were seen alive within 24 hours before the event.

Witnessed SCA are arrests occurring in the presence of a bystander or emergency personnel. **Unwitnessed SCA** was defined as a SCA which occurred in a person who was alone at the moment of the event and who was found unconscious or dead by a family member or neighbor, friend etc.
The 'Utstein Style' definitions (9) were used for basic CPR, advanced CPR and bystander CPR.
The Utstein recommendations for reporting on outcome of out-of-hospital SCA focuses on SCAs in which the EMS was involved. However, as Siscovick (6) mentions, when limiting data collection to information available through EMS data bases, comparison of outcomes across communities or over time will be biased. Therefore we included all witnessed and unwitnessed SCAs seen or not seen by the EMS.
Survival rate was defined as the number of SCA victims who were discharged alive from the hospital divided by the total number of SCAs (witnessed and unwitnessed) registered.
Resuscitation attempt rate was defined as the number of resuscitation attempts divided by the total number of SCA victims and
Resuscitation success rate was defined as the total number of hospital survivors divided by the total number of resuscitation attempts.

Statistical methods

All data were entered into the SPSS-pc statistical program. Statistical significance for differences have been tested by the Mann-Whitney-U test for continuous variables. When proportions showed a trend over the years, the chi-square test for trend was calculated. Furthermore 95% confidence intervals (CI) for proportions and their differences and for relative risk were calculated.

RESULTS

From January 1st, 1991 until December 31st, 1994 a total of 515 cases were included. Of these, 369 (72%) were men and 146 were women (28%) with a mean age of respectively 62.2 ± 8.9 and 62.7 ± 12.2 years.
Information about the victims medical history was obtained from the GPs and or hospital records in all 515 cases. A history of cardiac disease was present in 277 (53.8%) patients. Interestingly, in 53% of the women and in 44% of the men SCA was most likely the first manifestation of heart disease. Examination of GP and hospital records of all 277 cases known with a previous cardiac history showed that 177 (64%) victims were known with one or more previous myocardial infarctions (MI). The number of SCA victims with a previous MI decreased significantly over the years; 54/129 (42%) in 1991, 46/132 (35%) in 1992, 40/134 (30%) in 1993 and 37/120 (31%) in 1994 ($p<0.05$).
Time interval between the last MI and SCA was more than 2 years in 66% of the victims (mean 6.5 (± 5.3) years, median 5 years). In 131/177 victims known with a previous MI, a left ventricular ejection fraction (LVEF) was determined (post MI) by echocardiogram. The mean time interval between the last echocardiogram and SCA was 18.8 (± 21.2) months. In 56.5% victims a LVEF of more than 30% was present.

Yearly incidence of SCA

The mean yearly incidence of SCA in the age group 20-75 years was 129 SCA/132,762 mean population of the Maastricht region or 9.7/10,000 inhabitants. The yearly incidence of SCA was 9.8/10,000 in 1991, 9.9/10,000 in 1992, 10.1/10,000 in 1993 and 9.0/10,000 in 1994.
The prevalence of heart disease in the GP's network representative sample was 9,15%. When extrapolating this figure to our study population, the prevalence of heart disease was 9.15% of 132,762 is 12,148 inhabitants. It was estimated that the mean yearly incidence of SCA in inhabitants with a known cardiac disease was 53.8% of 129 = 69.4 / 12,147 or 57 / 10,000. A total of 120,615 inhabitants never had cardiac complaints or never sought medical

help for possible cardiac complaints. It was estimated that the mean yearly incidence of SCA in this group was 46.2% of 129 is 59.6 / 120,615 or 5/10,000 inhabitants. Therefore, it was estimated that the relative risk of SCA for persons with cardiac disease was about 11 (95% CI: 8 - 16).
In the age category 50-59 years, men with a previous cardiac history had a three times higher mean yearly incidence of SCA compared to women (60/10,000 vs 18/10,000). In men without a previous cardiac history between the ages of 50 and 59 years, the mean yearly incidence of SCA was 11/10,000 compared to 2/10,000 in women of the same age group.

Contribution of sudden death to total mortality

During the period January 1991 until January 1994, a total of 2030 inhabitants between 25 and 75 years of age died. In 375 inhabitants (18.5%) the mode of death was sudden. As shown in Table 1, this was 27% in men in the age group 55-64 years. In women, the highest percentage of SCA was found in the age categories 25-44 and 65-74 years (16%).

Site at the time of SCA

In 501/515 cases information on the location of the event was available. In 399 (79.6%) cases, SCA occurred at home and 102 (20.4%) outside home (Table 2).

Number of witnessed and unwitnessed sudden cardiac arrests

Of 30 victims it was not clear whether they were witnessed or unwitnessed and these cases were excluded. Of 485 victims, 293 (60.4%) were witnessed, 208 (71%) were at home and 85 (29%) outside home. Of those with SCA at home, the witness was a family member in 183 (88%) of cases. In 15 (7%) cases a friend and in 10 (5%) cases the general practitioner was present. Of the 85 witnessed SCAs outside home, 57 (67%) were witnessed by a bystander, 23 (27%) by a family member and 5 (6%) by a medical doctor or nurse. Not witnessed were 192 (39.6%) cases with 176 (91.7%) occurring at home.

Figure 1 gives a flow diagram of the 515 cases of SCA outside hospital, indicating the site of SCA, presence of a witness, incidence of a resuscitation attempt and by whom, and the number of patients discharged alive from hospital.

Table 1. Contribution of sudden death to total mortality in relation to gender in different age groups

	men			women		
Age (yrs)	all deaths	SD	%	all deaths	SD	%
25-44	97	8	8	68	11	16
45-54	139	29	21	82	7	8.5
55-64	351	95	27	169	21	12
65-74	713	137	19	411	67	16
Total	1300	269	21	730	106	14.5

Abbreviations: SD=sudden death; yrs=years; %=percentage of all deaths dying suddenly.

Table 2. Site of Sudden Cardiac Arrest (501 cases)

	N=501	%
At home	399	79.6
On the street	47	9.4
Public place	31	6.2
Other places	16	3.2
At the general practitioners home	4	0.8
At work	4	0.8

Resuscitation attempt, success and survival rates

1. Overall

In 16/485 sudden death cases it was not known whether or not resuscitation was attempted. Resuscitation was performed by the ambulance personnel and/or bystander in 237 (50.5%) cases. Of these, 32 (13.5%) were discharged alive from the hospital giving an overall survival rate of 32/515 = 6.2%.

2. Witnessed SCA

Of 11 witnessed SCA victims (9 at home, 2 outside) data on resuscitation were missing. In 210/282 (74.5%) witnessed cases resuscitation was attempted. Of these, 31 (14.8%) were discharged alive from the hospital. Survival from witnessed out-of-hospital SCA was therefore 31/293 = 10.6%.

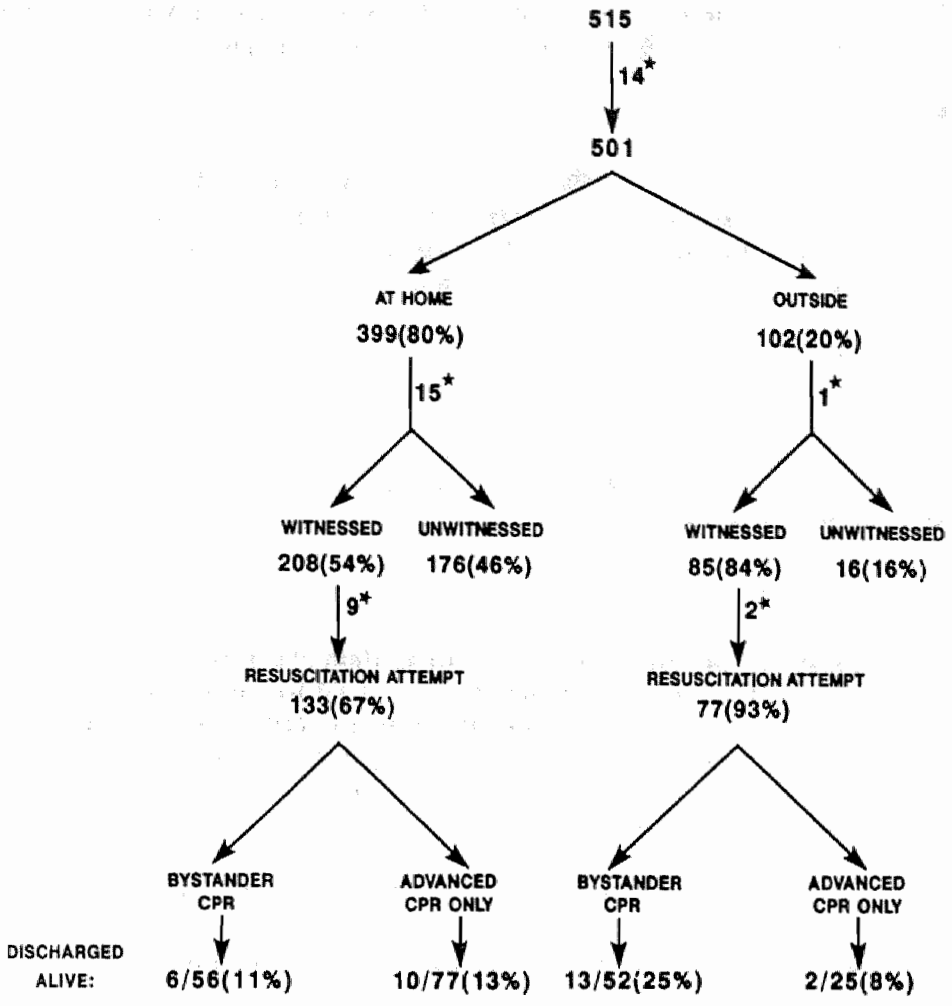

Figure 1. Flow diagram of the 515 cases of sudden cardiac arrest occurring outside hospital in the Maastricht area in the year 1991, 1992, 1993 and 1994. Information is incomplete or missing in cases indicated by an asterix. Note that in 80% of cases sudden cardiac arrest occurred at home with about half of them unwitnessed.

Witnessed SCA at home versus outside home

In 133/199 (66.8%) witnessed cases resuscitation was attempted at home and in 77/83 (92.7%) outside (95% CI: 15% - 37%). Between these two groups there were no significant differences in mean age and gender distribution. In 16/133 (12%) cases with a resuscitation attempt at home and 15/77 (19.5%) victims resuscitated outside were discharged alive from hospital (95% CI: -

2.5% - 17.5%). Therefore survival rates from witnessed SCA were 16/208 (7.7%) and 15/85 (17.6%) (95% CI: 2% - 18%) respectively.

Bystander CPR

At home, only 56 of 199 (28.1%) witnessed victims received bystander CPR. Outside, this occurred in 52/83 (62.6%) of cases (95% CI 22% - 47%). Success rates of CPR initiated by a bystander were 6/56 (10.7%) at home and 13/52 (25%) outside home (95% CI: 0% - 29%).

Advanced CPR

Of 77/199 (38.7%) victims who were at home and who received advanced CPR only, 10 (13%) were discharged alive. Of 25/83 (30.1%) victims outside home with only advanced CPR, 2 (8%) victims survived hospital admission. 95% CI were -3.7% to 21% and -9.5% to 19.5% respectively.

3. Unwitnessed SCA

In 5 cases with unwitnessed SCA at home, data about resuscitation were missing. In 27/187 (14.4%) unwitnessed victims resuscitation was attempted. At home in 21/171 (12.3%) and outside home in 6/16 (37.5%) victims (95% CI 7% to 43%). Only one victim (resuscitated at home) survived to hospital discharge. So survival from unwitnessed SCA at home was 1/176 (0.6%) and 0/16 (0%) outside (95% CI -6% to 18%).

Delays and cardiac rhythm at the time of the resuscitation attempt

The estimated overall mean time interval between the moment of collapse and the start of resuscitation was 5.3 $\pm$ 5.2 minutes at home and 3.9 $\pm$ 5.4 minutes outside ($p < 0.05$). When CPR was started by a bystander these values were 3 $\pm$ 3.2 minutes at home and 2.9 $\pm$ 2.7 minutes outside. The mean ambulance delay time was 6.4 $\pm$ 2.8 minutes at home and 6.5 $\pm$ 3.1 minutes outside.

In 310/515 (60.2%) victims an ambulance arrived at the scene. In 90 victims the ambulance personnel considered a resuscitation attempt no longer indicated. In 220 victims resuscitation was performed by the ambulance crew. In this latter group, the first documented rhythm was ventricular fibrillation (VF) in 120, ventricular tachycardia (VT) in 8, bradycardia in 30 and asystole in 62 victims.

Of 128 victims who were found in VT or VF, 29 (22.7%) survived to discharge and 3/92 (3.3%) (95% CI: 10% - 28%) victims with bradycardia or asystole.

DISCUSSION

Although the yearly incidence of out-of-hospital sudden coronary deaths seems to be declining (10), it continues to be a common cause of death. Our study, which is the first study on the incidence of out-of-hospital SCA performed in the Netherlands, shows that the mean yearly incidence of unexpected SCA was 1/1000 between the ages of 20 and 75 years and demonstrates that its contribution to total mortality in people between 25 and 75 years was nearly 19%. In men in the age group 55 to 64 years, 27% of all deaths occurred suddenly.

By restricting our cohort of interest to individuals younger than 75 years, we are aware of the fact that exclusion of a segment of the population that is prone to cardiac arrest may produce selection bias. However, we adjusted our denominator (all inhabitants between 20 and 75 years) in concordance with our numerator (all cases between 20 and 75 years) which is what Becker et al. (2) stated they were unable to do in their incidence study of 20 communities because data were unavailable. Furthermore we did not only include victims in whom the ambulance service was involved, but also those victims who were found dead. This may give better insight in the overall incidence and survival of SCA. However, the use of the '24 hour' definition will lead to the inclusion of unexpected SCAs caused by various causes such as ruptured abdominal aortic aneurysm and pulmonary embolism. A study by Pratt et al (11) showed that in a number of deaths that would have been classified as sudden cardiac based solely on temporal criteria, the cause of death at autopsy was non-cardiac. The yearly incidence of SCA with an underlying cardiac cause is therefore lower. Based on our autopsy data of 127 included SCA victims, it was estimated that about 20% of the total number of victims had a non-cardiac cause of SCA.

Like others (12-15), we found that 80% of the total number of SCAs occurred at home. Only 60% of the cardiac arrest victims were witnessed. Two third of the witnessed arrests took place at home, usually with a family member as witness. Of the unwitnessed arrests nine out of ten were at home. Only six percent of all out-of-hospital SCA cases were discharged alive from hospital. In our study, resuscitation was attempted in nearly 75% of the witnessed cases, with a higher incidence of CPR on the street and in public places than at home. In witnessed cases, resuscitation success rate was 12% at home and nearly 20% outside home. Differences in success rates at home vs outside home have also been reported by Ritter (13) and Litwin (14) (6% vs 13% and 13% vs 27% respectively). Most studies described improved outcome when the resuscitation attempt was started immediately by a witness before the ambulance arrived (16-24). Also in our study, the mean time interval between collapse and the start of the resuscitation attempt was shorter when sudden

cardiac arrest occurred outside as compared to at home (13, 14). The ambulance delay time was not different between witnessed cardiac arrest at home and outside. To our surprise, we found that at home, outcome of the resuscitation attempt was not different when CPR was started by a bystander or by the ambulance personnel. This is compatible with the hypothesis that resuscitation performance level is better among bystanders in the street than at home, perhaps because there is a far greater number of potential resuscitators available in public places. As shown by Gallagher (25) et al., effective bystander CPR is independently associated with a significant improvement in survival. A second explanation could be time-delay caused by the fact that family members who witnessed the event at home did not start resuscitation themselves but frequently called a neighbor or someone else to start resuscitation.

As previously reported (21), a rapid rhythm (VT or VF) at the time of the resuscitation attempt had a better prognosis than asystole or a slow rhythm. In our study it was estimated that the incidence of SCA is about eleven times higher in people with known cardiac disease as compared to asymptomatic men and women. Although this figure was estimated on the base of an extrapolation, it is very similar to the 9 times higher risk reported by Kannel (26). Furthermore most of these victims had a previous myocardial infarction. The mean time interval between MI and SCA was 6.5 years indicating that SCA frequently occurs late after MI. A low LVEF (<30%), which is known to be an important risk factor for SCA after MI (27,28,29), was present in less than half of the victims. Furthermore over the years, a decrease in the number of victims with a previous MI was observed. These findings in victims who were known with a previous MI together with the observation of absence of a previous cardiac history in 53% of the women and 44% of the men support the idea that even in the 1990s the majority of the SCA victims cannot be identified prior to the event.

To improve overall outcome of out-of-hospital SCA, thus decreasing the incidence of sudden death, emphasis should be on increasing both the number of resuscitation attempts and resuscitation success rate. The fact that in our study most witnessed sudden deaths occurred at home and that resuscitation attempt rate and success rate were low compared to those outside, indicates that emphasis should be on optimizing resuscitation efforts in the at home situation. Because our study shows that people with a history of heart disease had a higher chance of dying suddenly, we confirm the statement of Dracup et.al. (30) that family members of patients with cardiac disease is an important target group for training in cardiopulmonary resuscitation.

Furthermore we should also search for better telecommunication methods by developing small portable devices that transmit the occurrence of cardiac arrest to people that can help with basic and advanced cardiac life support.

To evaluate the effect of these measures and the value of primary and secondary prevention on the problem of SCA in the community, it is essential to continue to record all cases of witnessed and unwitnessed sudden death in the total population with and without a cardiac history. Furthermore, for comparison across communities it is important that studies concerning the incidence and overall outcome of SCA include all SCA victims and not only those in whom the EMSs are involved.

REFERENCES

1. Dahlberg ST. Gender difference in the risk factors for sudden cardiac death. Cardiology 1990;77(suppl 2):31-40.
2. Becker LB, Smith DW, Rhodes KV. Incidence of cardiac arrest: a neglected factor in evaluating survival rates. Ann Emerg Med 1993;22:86-91.
3. Vertesi L. The paramedic ambulance: A Canadian experience. Can Med Assoc J 1978;119:25-9.
4. Carveth SW, Olson D, Bechtel J. Emergency medical care system. Arch Surg 1974;108:528-30.
5. Bachman JW, McDonald GS, O'Brien PC. A study of out-of-hospital cardiac arrests in North-eastern Minnesota. JAMA 1986;256:477-83.
6. Siscovick D. Challenges in cardiac arrest research: data collection to assess outcomes. Ann Emerg Med 1993;22:92-8.
7. Composition of the population of the southern part of Limburg, the Netherlands 1991-1995, Central Statistical Office, Voorburg, the Netherlands.
8. Metsemakers JFM, Hoppener P, Knottnerus JA, Kocken RJJ, Limonard CBG. Computerized health information in the Netherlands: a registration network of family practices. Br J Gen Pract 1992;42:102-6.
9. Task force of representatives from the European Resuscitation Council, American Heart Association, Heart and Stroke Foundation of Canada, and Australian Resuscitation Council. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest (new abridged version The "Utstein Style"). Br Heart J 1992;67:325-33.
10. Goldberg RJ. Declining out-of-hospital sudden coronary death rates: additional pieces of the epidemiologic puzzle. Circulation 1989;79:1369-73.
11. Pratt CM, Greenway PS, Schoenfeld MH, Hibben ML, Reiffel JA. Exploration of the precision of classifying sudden cardiac death: implications for the interpretation of clinical trials. Circulation 1996;93:519-24.
12. Fitzpatrick B., Watt GCM, Tunstall-Pedoe H. Potential impact of emergency intervention on sudden deaths from coronary heart disease in Glasgow. Br Heart J 1992;67:250-4.
13. Ritter G, Wolfe RA, Goldstein S, et al. The effect of bystander CPR on survival of out-of-hospital cardiac arrest victims. Am Heart J 1985;110:932-7.
14. Litwin PE, Eisenberg MS, Hallstrom AP, Cummins RO. The location of collapse and its effect on survival from cardiac arrest. Ann of Emerg Med 1987;16:787-91.
15. Guzy PM, Pearse ML, Greenfield S. The survival benefit of bystander cardiopulmonary resuscitation in a paramedic served metropolitan area. Am J Public Health 1983;73:766-9.

16. Einarsson O, Jakobsson F, Sigurdsson G. Advanced cardiac life support in the prehospital setting: the Reykjavik experience. J Intern Med 1989;225:129-35.
17. Hoekstra J. Bystander CPR: a review. Resuscitation 1990;20:97-113.
18. Lund J, Skulberg A. Cardiopulmonary resuscitation by lay people, Lancet 1976;2:702-4.
19. Eisenberg M, Bergner L, Hallstrom A. Paramedic programs and out-of-hospital arrest II:impact on community mortality. Am J Public Health 1979;69:39-42.
20. Eitel DR, Walton SL, Guerci AD, Hess DR, Sabulsky NK. Out-of-hospital cardiac arrest: a six years experience in a suburban-rural system. Ann Emerg Med 1988;17:808-12.
21. Cummins RO, Eisenberg MS, Hallstrom AP, Litwin PE. Survival of out-of-hospital cardiac arrest with early initiation of cardiopulmonary resuscitation. Am J Emerg Med 1985;3:114-8.
22. Bossaert L, Van Hoeyweghen R and the Cerebral Resuscitation Study Group. Bystander cardiopulmonary resuscitation (CPR) out-of-hospital cardiac arrest. Resuscitation 1989;17:S55-S69.
23. Tweed WA, Bristow G, Donen N. Resuscitation from cardiac arrest: assessment of a system providing only basic life support outside of hospital. Can Med Assoc J 1980;122:297-300.
24. Copley DP, Mantle JA, Rogers WJ, Russel RO, Rackley CE. Improved outcome for prehospital cardiopulmonary collapse with resuscitation by bystanders. Circulation 1977;56:901-5.
25. Gallagher EJ, Lombardi G, Gennis P. Effectiveness of bystander cardiopulmonary resuscitation and survival following out-of-hospital cardiac arrest. JAMA 1995;274:1922-5.
26. Kannel WB, Schatzkin A. Sudden death: lessons from subsets in population studies. J Am Coll Cardiol 1985;5:141B-149B.
27. Bigger JT, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM and the Multicenter post-infarction research group. The relationship among ventricular arrhythmias, left ventricular dysfunction and mortality in the 2 years after myocardial infarction. Circulation 1983;69:250-8.
28. Shen WK, Hammill SC. Survivors of acute myocardial infarction: who is at risk for sudden cardiac death? Mayo Clin Proc 1991;66:950-62.
29. Fletcher RD. Sudden cardiac arrest after myocardial infarction. Drugs 1991;41:1-8.
30. Dracup K, Heakey DM, Taylor SE, Guzy PM, Breu C. Can family members of high risk patients learn cardiopulmonary resuscitation? Arch Intern Med 1989;149:61-4.

CHAPTER 9

Risk Indicators for Out-of-Hospital Cardiac Arrest in Coronary Artery Disease Patients

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ABSTRACT

Coronary artery disease (CAD) is the underlying cause of death in the majority of sudden cardiac arrest (SCA) victims. It is therefore of importance to identify risk factors for SCA in CAD patients.

From January 1991 to January 1994 all out-of-hospital SCA victims between the ages of 20 and 75 years and resident of the region of Maastricht were registered. A retrospective case-control study was performed consisting of a group of unselected SCA victims, with a clinical history of CAD, and a group of unselected age and sex matched CAD control patients living in the same region. Information about previous myocardial infarction (MI), left ventricular ejection fraction (LVEF), hypertension, hypercholesterolemia, diabetes mellitus, smoking, coffee and alcohol consumption was collected. A logistic regression model was fitted to all mentioned variables including age and sex.

Included were 117 SCA cases (84% men, mean age 65 years (± 7)) and 144 control patients (83% men, mean age 63 years (± 8)). Previous MI (Odds Ratio (OR) 4.0, 95% Confidence Interval (CI) 1.7 - 9.3), hypertension (OR 2.9, 95% CI 1.5 - 6.1), heavy coffee consumption (> 10 cups/day) (OR 55.7, 95% CI 6.4 - 483) and a LVEF < 40% (OR 11.2, CI 4.4 - 28.5) were independent risk indicators for SCA in CAD patients. Alcohol consumption (1-21 glasses/week) seemed to protect CAD patients from SCA (OR 0.5, 95% CI 0.2 - 0.98).

These observations suggest that changes in life-style factors can be of potential importance in protecting CAD patients from dying suddenly.

INTRODUCTION

Pathological studies have shown that coronary artery disease (CAD) is the underlying cause of death in the majority of sudden death victims (1,2). In the past, many efforts have been made to identify persons who are at high risk for sudden cardiac arrest (SCA) due to CAD. Despite claims that primary risk factors such as smoking, hypertension and hypercholesterolemia loose their significance in patients with CAD (3), several prospective studies (4-8) have shown that some classical risk factors also operate after clinical manifestations have developed. The risk of coffee and alcohol consumption on SCA in patients (men and women) with CAD is not well known.
In the present study we studied the role of alcohol and coffee consumption among other risk factors on SCA in patients with manifest CAD.

METHODS

Study population

In 1991 a registration network of out-of-hospital SCA in persons between 20 and 75 years was started in the southern part of South Limburg (region of Maastricht). This region encloses 203 square kilometers and has about 182,000 inhabitants of whom around 133,000 (73%) are between the age of 20 and 75 years. All SCA cases are reported by the general practitioners (GP), and personnel of the ambulance service located in the region. The ambulance personnel is contacted daily and the general practitioners once every week.

Case-control study

In this case-control study, only SCA victims known with a history of CAD to the cardiologist or GP were included. The control group was selected at random from the regional registration network of general practice (9). This data-base contains information about the medical history of a representative group of 12,061 inhabitants of the Maastricht area. The control group was frequency matched for age, gender and the presence of CAD. Control patients were residents of the same region and known to the GP and cardiologist with CAD. Included in the analysis were only those SCA victims of whom their close relatives were interviewed. To achieve comparability of information, relatives of control patients were interviewed.

Definitions and data collection

Sudden Cardiac Arrest

Sudden cardiac arrest was defined as unexpected, non traumatic loss of vital signs, such as consciousness, arterial pulse, blood pressure and respiration without preceding complaints or within 24 hours of the onset of complaints. Patients who were resuscitated successfully and unwitnessed victims in whom circumstances were pointing to an unexpected sudden death (for example those who died during sleep) were also included. Excluded were those in whom a circulatory arrest occurred because of a traumatic event, intoxication or in the terminal phase of another chronic disease. SCA victims who had a non-cardiac cause of death as determined by autopsy were also excluded from this case-control study.

Coronary Artery Disease

Coronary artery disease was defined as known with a previous (acute/silent) myocardial infarction (MI) and/or angina pectoris (stable or unstable). **Acute myocardial infarction** was diagnosed when the patient was admitted to the hospital with an electrocardiogram (ECG) showing the characteristic changes of a MI. Furthermore a typical rise of aspartate aminotransferase above the upper limit of normal (40 units per liter) was required. **'Silent' myocardial infarction** was considered to be present when the ECG or echocardiogram was diagnostic for an old MI without clinical documentation. **Stable angina pectoris** was defined as chest discomfort with or without irradiation occurring during the classical triggers for angina. **Unstable angina pectoris** (UAP) was diagnosed in the presence of crescendo angina (more severe, prolonged, or frequent) either of recent onset or superimposed on a preexisting pattern of relatively stable exertion-related angina pectoris (10). Previous cardiac history was defined as known with angina pectoris (stable/unstable), myocardial infarction, heart failure, valvular disease, arrhythmias or other heart diseases.

The partner or a close relative of all SCA cases and CAD controls received a letter, signed by their general practitioner, asking permission for an interview. Family members of SCA victims were called one week after they received this letter. When the family member agreed, he or she was interviewed. Reasons for refusal were noted. Relatives of control patients were interviewed after written permission by the control patient. Interviews were carried out by the investigators or trained interviewers. A questionnaire was used to obtain information about presence or absence of risk factors. The general practitioners of all SCA cases and controls were also asked by questionnaire whether the patients were *known with* hypertension,

hypercholesterolemia or diabetes mellitus. These data were also checked from hospital charts and out-patient clinic records.
Hypertension was defined as a systolic blood pressure ≥ 160 mm Hg and/or a diastolic blood pressure ≥ 95 mmHg (11). **Hypercholesterolemia** was defined as having a serum cholesterol ≥ 6.5 mmol/l (12) and /or treatment by GP or cardiologist. **Diabetes mellitus** was considered to be present if either type I (insulin dependent diabetes mellitus) or type II (non-insulin dependent diabetes mellitus) was diagnosed. Hetero-anamnestic information about other risk factors such as smoking, alcohol and coffee consumption was obtained from the interview by using a questionnaire. Concerning **smoking** three categories were defined: never-smokers, ex-smokers and current smokers. Information on **alcohol-intake** was collected using three questions. First, whether or not the victims or control patient used to consume alcoholic drinks; second, if the answer was 'yes', what kind of alcoholic beverage (the categories were beer, wine or spirits), and third, how many units of alcoholic drinks were consumed on average in a week. Concerning **coffee** (with caffeine) consumption, the number of cups consumed per day was obtained and registered according to five categories: 1) no coffee 2) 1 thru 3 cups / daily 3) 4 thru 6 cups / daily 4) 7 thru 10 cups / daily 5) more than 10 cups a day.
Left ventricular ejection fractions (LVEF) were obtained from the echo reports which reported on the results of the last echocardiogram which was made in cases and controls. Three categories were defined: 1. LVEF ≥ 40%, 2. LVEF < 40% and 3. no echocardiogram made.

Statistical methods

All data were analyzed using the SPSS-pc statistical program. Statistical significance for differences have been tested by chi-square test for proportions and Mann-Whitney-U test for continuous variables. A p-value < 0.05 was considered as statistically significant.
Multiple logistic regression analysis was performed to analyze the relation of the four major primary risk factors hypertension, hypercholesterolemia, diabetes mellitus and smoking (never, ex and current smoking) and previous MI (independent variables) with SCA (dependent variable), simultaneously taking the influence of all risk factors into consideration. The matching factors age and sex were included in the regression model. In a second model the influence of coffee and alcohol consumption were studied. In a third model LVEF was added. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated.

RESULTS

During a period of three years (1991-1993) a total of 372 out-of-hospital SCA victims were registered. Of these, 206 (55.4%) had a previous cardiac history of whom 168 had CAD (137 (81.5%) men, mean age 65 (± 7) years, 138 (82.1%) previous MI). A total of 240 sex and age frequency matched CAD control patients (190 men (79.2%), mean age 63 (± 9) years, 116 (48.3%) previous MI) were selected at random from the general practitioners database.

Relatives of 117 (69.6%) SCA victims with CAD and relatives of 144 (60%) CAD control patients were interviewed and included in the case-control study. Cases and controls were representative for the total group of SCA victims with CAD (n=168) and CAD control patients (n=240) according to age, gender and the presence of a previous MI.

In 77/117 (65.8%) cases a witness was present at the moment of SCA. Of all 117 victims, 72 died unexpected without preceding complaints or within 1 hour of the onset of complaints, in 17 victims complaints were present for more than one hour before the event and in 28 victims, it was unknown whether they had complaints before their demise.

Coronary artery disease

Table 1. shows that there were no significant differences in mean age and gender distribution between included cases and controls. There was a significant higher number of cases who had an MI in their past medical history in comparison with the control group (83% versus 52%).
Of those cases with a previous MI, 64 (66%) cases had one MI while 33 (34%) cases had two or more MIs in the past. In the control group these figures were 59 (79%) and 16 (21%) respectively making this subdivision not significantly different from the case group. Between cases and controls, there was also no significant difference in the distribution of the years in which the last MIs occurred (Table 1) and in the number of hospital admissions with unstable angina. The number of patients with LVEF < 40% was significantly higher in the case group compared with the control group.

Table 1. Gender, age and medical history of SCA cases and controls.

	SCA cases N=117	controls N=144	P-value
Gender			
men	98 (84%)	119 (83%)	
women	19 (16%)	25 (17%)	ns
Age			
20-57 years	20 (17%)	33 (23%)	
58-64 years	30 (26%)	36 (25%)	
65-69 years	30 (26%)	36 (25%)	
70-74 years	37 (31%)	39 (27%)	ns
Unstable AP	44 (38%)	61 (42%)	ns
MI	97 (83%)	75 (52%)	<0.001
Year of last MI			
1970-1979	12 (12%)	10 (13%)	
1980-1989	46 (47%)	40 (53%)	
1990-1993	21 (22%)	20 (27%)	ns
unknown	18 (19%)	5 (7%)	
LVEF			
< 40%	53 (45%)	15 (10%)	
≥ 40%	33 (28%)	75 (52%)	
unknown	31 (27%)	54 (38%)	<0.001

SCA = sudden cardiac arrest; AP = angina pectoris; MI = myocardial infarction. LVEF=left ventricular ejection fraction.

Risk factors

Univariate analysis as presented in Table 2 shows that there were no significant differences between cases and controls in the number of patients known with hypercholesterolemia and diabetes mellitus. However, the number of patients known with hypertension and the number of active smokers was higher in the case group, whereas the number of ex-smokers was significantly higher in the control group.

In both groups, most patients consumed coffee. However, in the case group the number of 'heavy' coffee drinkers (>10 cups/day) was higher compared with the control group.

In the control group, more patients consumed alcohol compared with the case group and this was also true for all three types of alcoholic beverages (beer, wine and spirits) (not shown). The number of units per week was also significantly higher in the control group, most evident for the category 1 to 6 glasses per week.

Table 2. Risk factors

		SCA cases N=117	controls N=144	P-value
Hypertension	yes	53 (45%)	36 (25%)	<0.001
	no	64 (55%)	108 (75%)	
Hypercholesterolemia	yes	33 (28%)	55 (38%)	0.11
	no	84 (72%)	89 (62%)	
Diabetes Mellitus	yes	16 (14%)	10 (7%)	0.11
	no	101 (86%)	134 (93%)	
Smoking	yes	46 (39%)	34 (24%)	0.02
	stopped	54 (46%)	88 (61%)	
	never	17 (15%)	22 (15%)	
Coffee	0 c/d	8 (6.8%)	13 (9.0%)	<0.001
	1-3 c/d	35 (29.9%)	45 (31.3%)	
	4-6 c/d	31 (26.5%)	58 (40.3%)	
	7-10 c/d	15 (12.8%)	26 (18.0%)	
	>10 c/d	23 (19.7%)	2 (1.4%)	
	unknown	15 (4.3%)	0	
Alcohol	0 gl/w	58 (49.6%)	47 (32.6%)	<0.01
	1-6 gl/w	17 (14.5%)	44 (30.6%)	
	7-21 gl/w	24 (20.5%)	43 (29.9%)	
	>21 gl/w	15 (12.8%)	9 (6.3%)	
	unknown	3 (2.6%)	1 (0.6%)	

SCA = sudden cardiac arrest; gl/w = glasses/week; c/d = cups/day

Independent risk indicators for SCA

Logistic regression analysis of the four major risk factors and a history of MI, shows that known with diabetes mellitus, hypertension and previous MI were independently associated with SCA. (Table 3, model 1). When alcohol and coffee consumption were also included in the model, diabetes mellitus did not appear to be an independent risk indicator anymore. The extended regression model (Table 3, model 2) shows strong independently positive associations of hypertension, previous MI and coffee consumption of more than 10 cups a day with SCA. Alcohol consumption of 1-21 glasses per week was negatively associated with SCA (Table 3, model 2).

Table 3. Results of multiple logistic regression analysis, with SCA as the dependent variable and 3 sets of independent variables (model 1,2,3).

Variables included in the model	Model 1* (OR - 95% CI)	Model 2** (OR - 95% CI)	Model 3*** (OR - 95% CI)
Hypertension	2.3 (1.3 - 4.1)	2.5 (1.3 - 4.9)	2.9 (1.5 - 6.1)
Hypercholesterolemia	0.7 (0.4 - 1.3)	0.7 (0.3 - 1.3)	0.7 (0.4 - 1.6)
Diabetes Mellitus	2.9 (1.1 - 7.6)	2.0 (0.6 - 6.1)	2.2 (0.7 - 7.1)
Smoking			
ex smoker	0.8 (0.3 - 2.0)	0.6 (0.2 - 1.8)	0.5 (0.15 - 1.6)
current smoker	1.7 (0.7 - 4.4)	0.9 (0.2 - 1.8)	0.9 (0.30 - 3.1)
MI	4.8 (2.5 - 9.3)	7.7 (3.5 - 17.2)	4.0 (1.7 - 9.3)
Coffee consumption			
1-3 c/d		2.3 (0.7 - 8.0)	2.8 (0.6 - 12.6)
4-6 c/d		1.3 (0.4 - 4.3)	1.8 (0.4 - 7.9)
7-10 c/d		1.4 (0.4 - 5.2)	2.0 (0.4 - 10.5)
>10c/d		27.3 (3.8 - 198)	55.7 (6.4 -482.8)
Alcohol consumption			
1-21 gl/w		0.5 (0.2 - 0.9)	0.5 (0.2 - 0.98)
>21 gl/w		2.1 (0.6 - 6.8)	1.2 (0.4 - 4.4)
LVEF			
< 40%			11.2 (4.4 - 28.5)
no echocardiogram			1.2 (0.6 - 2.7)

* including hypertension, hypercholesterolemia, diabetes mellitus, smoking and previous myocardial infarction (and both matching factors age and sex).
** as model 1 and additionally including coffee and alcohol consumption.
*** as model 2 and additionally including left ventricular ejection fraction (LVEF)
non-smoking as reference category; coffee, alcohol consumption 0 units/week = reference category; LVEF $\geq$ 40% as reference category

Current smoking tended to be a risk indicator for SCA (OR 2.1, (0.9-5.6)) in a model in which only hypertension, hypercholesterolemia, smoking and diabetes mellitus were included, but was no longer a risk indicator in the extended model (Table 3, model 1). Ex-smoking was also not associated with SCA and it did not make any difference whether smoking was stopped more or less than 10 years ago.

Table 4. Relation between previous myocardial infarction and smoking in *CAD controls*

Smoking	Previous myocardial infarction	
	yes N=75	no N=69
never	8%	23%
stopped	61%	61%
current	31%	16%

Table 5. Relation between smoking and alcohol consumption and smoking and coffee consumption in *CAD cases*

Smoking	alcohol consumption			coffee consumption		
	no N=58	1-21 gl/w N=41	>21 gl/w N=15	no N=8	1-10 c/d N=81	>10 c/d N=23
never	26%	5%	0%	37.5%	15%	9%
stopped	36%	58.5%	47%	25%	54%	26%
current	38%	36.5%	53%	37.5%	31%	65%

gl/w = glasses per week; c/d = cups per day

Univariate analysis shows that there was a significant association between smoking and previous MI in the control group (p=0.013) but not in the case group (Table 4). Controls with an MI were more often current smokers while those without an MI were more often never-smokers. There were also significant associations between alcohol consumption and smoking (p=0.011) and between coffee consumption and smoking (p=0.013) in the case group but not in the control group (Table 5). Heavy alcohol and coffee consumers were also often current smokers, whereas moderate alcohol and coffee consumers were more often ex-smokers. Logistic regression analysis showed no significant interactions between smoking and these three mentioned variables in their association with SCA.

The third model (Table 3) shows that LVEF of less than 40% was positively associated with SCA. Furthermore it shows that LVEF was a confounder for the effect of previous MI, coffee and heavy alcohol consumption.

DISCUSSION

In a retrospective unselected case-control study we investigated classical risk factors and alcohol and coffee consumption for unexpected SCA in patients known with CAD. Our study showed that hypertension, previous MI, LVEF < 40% and heavy coffee-intake (>10 cups/day) seem to be important risk indicators for SCA while alcohol intake (1-21 glasses/week) appears to protect them from SCA.

Hypertension is known to be an important risk factor for developing CAD and sudden death in men without prior CAD (13,14). In our study, CAD patients with hypertension in their medical history appear to almost triple their risk for SCA compared with those not known with hypertension. In the literature the role of hypertension in relation to SCA is not quite clear. Prospective studies (15,16) stated that blood pressure had less impact on new CAD events and CAD mortality in CAD patients, but studies performed by Heliovaara (5) and Wilhelmsen (17) showed the opposite. In a prospective study by Suhonen (18), higher blood pressure did not increase the risk of sudden coronary death significantly, but appeared to increase the incidence of non-sudden death.

In our study, known with hypercholesterolemia was not an independent risk indicator for SCA. This can be due to the possibility that cholesterol, in contrast to blood pressure, may not have been routinely measured in all CAD patients. Results from studies by Suhonen (18) and Heliovaara (5) indicate that in men with pre-existing ischemic heart disease the serum concentration of cholesterol remains of prognostic importance for sudden coronary death and total CAD mortality.

Diabetes is a well known risk factor for the development of CAD and as shown by Butler et al. (19) even a significant risk factor for CAD mortality in persons not known with CAD. In our CAD patients, diabetes mellitus showed to be a significant risk indicator for SCA independent of hypertension, hypercholesterolemia, smoking and previous MI.

Cigarette smoking is another important classical risk factor for MI and sudden coronary death (20). Several studies (21, 22) showed that cigarette-smoking significantly worsened the long-term prognosis after myocardial infarction. Suhonen et al (18) reported that it was a significant risk factor for sudden coronary death in men with manifest CAD. In our study, current smoking tended to be a risk factor for SCA independent of hypertension, hypercholesterolemia and diabetes mellitus. When previous MI was added to the model (model 1), the effect of smoking in our study was reduced. This may in part be due to a lack of power since the strength of the effect was not drastically reduced after additional adjustment for MI, but may also be explained by the association between smoking and previous MI in the control group. Coffee and alcohol consumption were important confounders for the effect of current smoking on SCA. However, independent effects of

smoking, alcohol and coffee consumption on the risk of SCA are difficult to disentangle since these factors were strongly related to one another. Therefore we have to be cautious in interpreting the role of cigarette smoking in the fully adjusted model.

Consumption of coffee has a positive association with serum cholesterol concentration (23). Furthermore, it is presumed that caffeine causes cardiac arrhythmias or increases heart rate (24). Many studies have investigated coffee consumption as a risk factor for CAD and overall CAD mortality (25-29), but to our knowledge, the risk of coffee consumption on sudden death in CAD patients has not been studied. Our study showed that heavy coffee consumption appeared to be significantly related to SCA. A recent meta-analysis on the effect of coffee on MI and death from CAD showed discrepancies between several cohort studies (30). In the Framingham study (26), multivariate analysis for individuals with pre-existing cardiovascular disease showed no association between coffee-intake and cardiovascular disease. A study by Stensvold et al (31) showed an increased risk of coronary death during the first six years of follow-up in persons without CAD. An increased risk was only found in those who drank nine cups a day or more what is in accordance with our findings in CAD patients on the risk of SCA. One can only speculate on the role of the strength of the coffee in different countries!

The intake of one or two alcoholic beverages a day is associated with the lowest risk of CAD and CAD mortality (32-37). In a study by Shaper et al (37), men with symptomatic CAD showed a strong inverse association between moderate alcohol consumption and all major and fatal CAD events. In our study alcohol-intake of 1 to 21 glasses per week was associated with a reduced risk of SCA in CAD patients. Low alcohol-consumption (1 to 6 glasses a week) also appeared to be protective against SCA. Alcohol-intake of more than 21 glasses per week increased the risk of SCA in CAD patients, however this was not significant and the effect diminished when LVEF was added to the model probably because of the presence of a relation between heavy alcohol consumption and a low LVEF. A study by Lithell (38), however, showed a strong association between heavy alcohol consumption and sudden death. The mechanism by which moderate alcohol-intake 'protects', remains unclear. Steinberg (39) suggests that the best hypothesis probably relates to the increased concentration of high-density lipoprotein (HDL) cholesterol. According to Renaud (40), moderate alcohol intake does not prevent CHD through an effect on HDL cholesterol but rather through a hemostatic mechanism. Platelet aggregation is inhibited significantly by alcohol intake levels associated with the reduced risk of CHD (40).

The presence of a previous MI and a LVEF of less than 40% were positively associated with SCA.

Limitations of our study

The design of this study has the limitation that causal inferences can not be made. Therefore risk factors have to be interpreted as risk indicators for SCA instead of causally related factors. Also the retrospective nature may have hampered accurate information on blood pressure values and cholesterol levels in the past. In contrast to prospective studies, we can only report on the risk of hypertension and hypercholesterolemia in the medical history of CAD patients.

The non response rate among cases was 30%. The most frequent reason for refusing participation was the fact that the next-of-kin of SCA cases did not want to be confronted again with the painful situation of losing their beloved. The non response rate among controls was 40% and the most important reason for non-response was the fact that they did not want to burden their family members.

There was no obvious evidence for selection bias because the included cases and controls did not differ from the total case and control groups according to the variables age, gender and the mode of CAD (MI, UAP). Furthermore, there was no significant difference between cases and controls in education level ($p=0.2$) and this was not a confounder in the regression model (results not shown).

The hetero-anamnestic design was chosen to gain comparable information about the risk factors smoking, alcohol-intake and coffee-consumption of both cases and controls. The information may be biased by the fact that the memory of family members may be selective and may be influenced by social values especially regarding alcohol-consumption.

Another point which has to be discussed is our use of the '24 hours' definition of SCA to include not only witnessed but also unwitnessed unexpected deaths. We are aware of the fact that this broad definition can lead to the inclusion of unexpected but less sudden deaths and deaths of non-cardiac cause. However, an autopsy study on 127 (witnessed and unwitnessed) out-of-hospital SCA victims showed that in 38/40 (95%) victims with a history of CAD, the cause of death was cardiac.

Significance of our findings

Physicians looking after patients with CAD are helped when they are able to identify patients at high risk for unexpected SCA. Unfortunately, risk stratifying tests, currently available and performed at the time of discharge from the hospital after myocardial infarction, have a low positive predictive accuracy (41). Informing CAD patients about the values and the risks of alcohol and coffee consumption may be of help to reduce SCA in these patients.

REFERENCES

1. Davies MJ. Pathologic view of sudden cardiac death. Br Heart J 1981;45:88-96.
2. Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. in:Braunwald E, ed Heart disease: a textbook of cardiovascular medicine. Philadelphia: WB Saunders Company, 1992:756-83.
3. Schatzkin A, Cuppes L, Heeren T, Monelock S, Kannel W. Sudden death in the Framingham Heart Study. Am J Epidemiol 1984;120:888-99.
4. Rose O, Reid DD, Hamilton PJS, McCartney P, Keen H, Jarrett RJ. Myocardial ischaemia, risk factors and death from coronary heart disease. Lancet 1977;1:105-9.
5. Heliovaara M. Importance of coronary risk factors in the presence or absence of myocardial ischaemia. Am J Coll 1982;50:1248-52.
6. Shaper AG, Pocock SJ, Walker M et al. Risk factors for ischaemic heart disease: the prospective phase of the British Heart Study. J Epidemiol Community Health 1985;39:197-209.
7. Romo M. Factors related to sudden death in acute ischemic heart disease: a Community study in Helsinki. Acta Med Scand 1973;5:47-51.
8. Kannel WB, Doyle JT, Mcnamara P, Quickenton P, Gordon T. Precursors of Sudden coronary death: factors related to the incidence of sudden death. Circulation 1975;51:606-13.
9. Metsemakers JFM, Höppener P, Knottnerus JA, Kocken RJJ, Limonard CBG. Computerized health information in the Netherlands: a registration network of family practices. Br J Gen Pract 1992;42:102-6.
10. Rutherford JD, Braunwald E. Chronic Ischemic Heart Disease. In: Braunwald E, Heart disease: a textbook of cardiovascular medicine. Philadelphia: WB Saunders Company, 1992;1293,1334.
11. Final Report of the Working Group on High Blood Pressure. An epidemiological approach to describing risk associated with blood pressure levels. Hypertension 1985;7:457-68.
12. Anonymous. Netherlands Cholesterol Consensus Update. Hart Bulletin 1992;23:9-21 (in Dutch).
13. Kannel WB, Thomas HE Jr. Sudden coronary death: the Framingham study. Ann NY Acad Sci 1982;382:3-20.
14. Chiang BN, Perlman LV. Fulton M, Ostrander LD, Epstein FH. Predisposing factors in sudden cardiac death in Tecumseh, Michigan: a prospective study. Circulation 1970;41:31-7.
15. Phillips AN, Shaper AG, Pocock SJ, Walker M, Macfarlane PW. The role of riskfactors in heart attacks occurring in men with pre-existing ischaemia heart disease. Br Heart J 1988;60:404-10.
16. Coronary Drug Project Research Group. Implications of findings in Coronary Drug Project for secondary prevention trials in coronary heart disease. Circulation 1981;63:1342-50.
17. Wilhelmsen L. Primary and secondary prevention. J Hypertens 1987;5:79-82.
18. Suhonen O, Reunanen A, Knekt P, Aromaa A. Risk factors for sudden and non-sudden coronary death. Acta Med Scand 1988;223:19-25.
19. Butler WJ, Ostrander LD Jr, Carman WJ, Lamphiear DE. Mortality from coronary heart disease in the Tecumseh study: long-term effect of diabetes mellitus, glucose tolerance and other risk factors. Am J Epidemiol 1985;121:541-7.
20. Wilhelmsen L. Coronary heart disease: epidemiology of smoking and intervention studies of smoking. Am Heart J 1988:115:242-9.

21. Sparow D, Dawber TR. The influence of cigarette smoking on prognosis after a first myocardial infarction. J Chronic Dis 1978;31:425-32.
22. Coronary Drug Project Research Group. Cigarette smoking as a risk factor in men with a prior history of myocardial infarction. J Chronic Dis 1978;32:415-25.
23. Aro A. The effect of coffee on serum lipids and its clinical considerations. Cardiovasc Risk Factors:1993;3:238-243.
24. Myers MG. Caffeine and cardiac arrhythmias. Ann Int Med 1991;114:147-150.
25. Lacroix AZ, Mead LA, Liang KY, Bedell TC, Pearson TA. Coffee consumption and the incidence of coronary heart disease. N Engl J Med 1986;315:977-82.
26. Wilson PWF, Garrison RJ, Kannel WB, McGee DL, Castelli WP. Is coffee consumption a contributor to cardiovascular disease? Insights from the Framingham study. Arch Intern Med 1989;149:1169-72.
27. Rosengren A, Wilhelmsen L. Coffee, coronary heart disease and mortality in middle-aged Swedisch men: findings from the Primary Prevention Study. J Intern Med 1991;230:67-71.
28. Tverdal A, Stensvold F, Solvoll K, Foss OP, Lund-Lansen P, Bjartveit K. Coffee consumption and death from coronary heart disease in middle aged Norwegian men and women. Br Med J 1990;300:566-9.
29. LeGrady D, Dyer AR, Shekelle RB, et al. Coffee consumption and mortality in the Chicago Western Electric Company Study. Am J Epidemiol 1987;126:803-12.
30. Greenland S. A meta-analysis of coffee, myocardial infarction, and coronary death. Epidemiology 1993;4:366-74.
31. Stensvold I, Tverdal A, Jacobsen BK. Cohort study of coffee intake and death from coronary heart disease over 12 years. Br Med J 1996;312:544-5.
32. Moore RD, Pearson TA. Moderate alcohol consumption and coronary artery disease. A review. Medicine 1986;65:242-67.
33. Maclure M. Demonstration of deductive meta-analysis; ethanol intake and risk of myocardial infarction. Epidemiol Rev 1993;15:328-51.
34. Klatsky AL, Armstrong MA, Friedman GD. Alcohol and mortality. Ann Intern Med 1992;117:646-54.
35. Hennekens CH, Willett W, Rosner B, Cole D, Mayrent SL. Effects of beer, wine, and liquor in coronary deaths. JAMA 1979;242:1973-4.
36. Grohbaek M, Deis A, Sorensen TIA, Becker U, Schnohr P, Jensen G. Mortality associated with moderate intake of wine, beer, or spirits. Br Med J 1995;310:1165-9.
37. Shaper AG, Wannamethee G, Walker M. Alcohol and coronary heart disease: a perspective from the British Regional Heart Study. Int J Epidemiol 1994;23:482-94.
38. Lithell H, Aberg H, Selinus I, Hedstrand H. Alcohol intemperance and sudden death. Br Med J 1987;294:1456-58.
39. Steinberg D, Pearson TA, Kuller LH. Alcohol and atherosclerosis. Ann Intern Med 1991;114:967-76.
40. Renaud S, De-Lorgeril M. Wine, alcohol, platelets, and the French paradoxfor coronary heart disease. Lancet 1992;339:1523-6.
41. Wellens HJJ, de Vreede J, Gorgels APM. Sudden cardiac death: how to reduce the number of victims? Eur Heart J 1995;16G:7-9.

CHAPTER 10

Autopsy Findings in Out-of-Hospital Cardiac Arrest Victims With and Without a Previous Cardiac History

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ABSTRACT

Autopsy findings are described in people with and in those without a previous cardiac history who died suddenly out-of-hospital and who were included in a prospective population-based sudden cardiac arrest (SCA) registry in the Maastricht area in the Netherlands.

From January 1st 1991 till December 31 1994 autopsies were performed on 127/483 (26%) SCA victims. Of these 94 (74%) were men and 33 (26%) were women. Mean age was 58 (± 12) years and in 87 (68.5%) cases SCA was witnessed. A cardiac cause of sudden death was found in 50/53 (94%) victims with and in 46/74 (62%) victims without a previous cardiac history ($p<0.001$). Coronary artery disease was the cause of death in 94/96 (98%) victims while pulmonary embolism and aortic hemorrhage were the most important reasons in victims in whom no cardiac cause was found, each occurring in one third of these cases.

Extent of coronary artery disease was not different between victims with a previous cardiac history and those without a previous cardiac history. Single, two, three and four vessel disease was found in respectively 11,16,18 and 1 patients with and in respectively 12,16,12 and 2 patients without a previous cardiac history.

However, healed myocardial infarction (MI) and cardiomegaly were significantly more often present in victims with a previous cardiac history; 36 (75%) versus 15 (33%, $p<0.05$) and 45 (94%) versus 34 (74%, $p<0.05$) respectively. A recent MI was present in 25 (52%) victims with and in 30 (65%) without a cardiac history (ns).

On the basis of the autopsy data it was estimated that in our community the yearly incidence of sudden death with a cardiac cause was 7/10.000 inhabitants between the ages of 20 and 75 years.

In conclusion, at autopsy a cardiac cause for sudden death was more frequently found in SCA victims with a cardiac history compared with those without a previous cardiac history. Although an old MI and cardiomegaly were significantly more often found in the group of sudden coronary death victims with a previous cardiac history, they were also often present in victims without a cardiac history. The number of significantly narrowed coronary arteries and the incidence of a recent MI were not different between the two groups. This suggests that in both groups, sudden death was often caused by a recent ischemic event.

INTRODUCTION

Out-of-hospital sudden death is a frequent mode of death not only in patients known with heart disease but also in apparently 'healthy' persons. In this latter group it is often the first symptom of an underlying heart disease, usually coronary artery disease (1,2). Many autopsy studies have focused on pathological findings in the coronary arteries and myocardium of selected groups of sudden coronary death victims (3,4,5,6). In the present study we studied and compared causes of sudden death between autopsied victims with and those without a previous cardiac history. All victims were prospectively included in a population based study on out-of-hospital sudden cardiac arrest in the Maastricht area.
Because there are no data on the incidence of cardiac disease as cause of out-of-hospital sudden death in the Netherlands, we estimated the incidence of sudden cardiac death based on the autopsy findings.

METHODS

Study population

During a four year period (January 1st, 1991-December 31 st, 1994) 515 victims of unexpected out-of-hospital SCA between the age of 20 and 75 years and living in the region of Maastricht in the Netherlands were registered. The area encloses 203 square kilometers and has approximately 182,000 inhabitants of whom around 133,000 (73%) are between the age of 20 and 75 years.

Definition of sudden cardiac arrest

Sudden cardiac arrest was defined as unexpected, non-traumatic loss of vital signs, such as consciousness, arterial pulse, blood pressure and respiration without preceding complaints or within 24 hours of the onset of complaints. Witnessed SCAs are arrests occurring in the presence of a bystander or emergency personnel. Unwitnessed SCA was defined as a SCA which occurred in a person who was alone at the moment of the event and who was found unconscious or dead by a family member or neighbor, friend etc.

Inclusion and exclusion criteria

Included in this study were all witnessed and unwitnessed victims between the age of 20 and 75 in whom an autopsy was performed. Excluded were patients with a circulatory arrest following a traumatic event or intoxication or with SCA occurring in the terminal phase of a chronic disease.

The age limit of 75 years was chosen because inhabitants who are above this age are often living alone, limiting the possibility to obtain information about circumstances of death and complaints preceding the event and to get permission to perform autopsy.

Data collection

All out-of-hospital SCA victims were reported by the general practitioners in the region and the ambulance personnel. The ambulance service was contacted daily and all general practitioners were phoned every week. Patients age, gender and data about complaints and circumstances surrounding SCA were obtained from a questionnaire filled out by the personnel of the ambulance service and or by interviewing the general practitioner and the victim's family when possible.
Information about the medical history of all autopsied and non-autopsied victims was obtained from the patient chart of the general practitioner and from hospital reports when present. A previous cardiac history was defined as known with a history of myocardial infarction, stable or instable angina pectoris, valvular disease, heart failure, rhythm disturbances or other heart diseases.
Permission to perform autopsy was obtained from the family by the attending general practitioner in cases who were found dead or were not transported to the hospital or by the cardiologist when the victim died in the hospital emergency room after unsuccessful resuscitation.
From January 1st 1991 till January 1st 1995, 515 SCA cases (60% witnessed) were included. Of these 32 were successfully resuscitated. Autopsy was performed on 127/483 (26%) victims.

Autopsy protocol and definitions

All autopsies were performed by staff members of the department of pathology in the Academic Hospital of Maastricht using a standardized protocol.
All hearts were excised and weighed without the aortic root. Cardiomegaly was considered to be present when the heart weight was more than 400 grams (3).
The left main (LM) coronary artery, the left anterior descending (LAD), the left circumflex branch (CX) and the right coronary artery (RCA), were cross sectioned at 5 mm intervals along their course by one pathologist (MD) who did not know the autopsy findings and the medical history of the victims. Findings are presented in relation to the 4 coronary arteries (LM,LAD,CX and RCA). Of each coronary artery the segments with the most important stenoses (>50% narrowed) were excised and fixed in 10% phosphate buffered formalin (pH 7.4), decalcified if necessary, dehydrated with alcohol and

xylene and embedded in paraffin using routine procedures. Subsequently 4 µm sections were cut and stained by the hematoxylin or elastica van Gieson technique. The percentage of narrowing of the intraluminal diameter of the artery segments were determined by computerized morphometry (Quantimet 570, Leica). A coronary artery (including the LM) with a narrowing of more than 75% of the total intraluminal diameter (3,4) caused by atheroma and or a thrombus was considered to be significantly narrowed. Transversal slices were cut every 0.5 cm from the apex to the base of the heart and were macroscopically searched for scars. Recent myocardial infarction (MI) was diagnosed by the Nitro Blue Tetrazolium (NBT) staining method, which enables to identify an infarction 4-6 hours after its onset (7). A healed myocardial infarction was diagnosed when a fibrous scar was seen. It was assumed that sudden death was due to coronary artery disease when one or more significantly narrowed coronary arteries were present and/or a myocardial infarction (recent or healed) was found in the absence of a non-cardiac cause of death.

Estimation of total number of sudden cardiac deaths

During a period of four years a total of 483 sudden death victims were included. Of these 342 (71%) were men and 141 (29%) were women, the mean age was 62.7 (± 9.8) years and 54% of the victims had a previous cardiac history.
In the age group of 20 to 50 years, autopsy was performed in 33 of 54 (61%) sudden death victims. According to sex, mean age and presence or absence of a cardiac history, this autopsied group was representative for the total group of victims (Table 1).
In the age category 50-75 years, autopsy was performed on 94 of 429 (22%) victims. The mean age and the number of victims with a previous cardiac history in this autopsied group were significantly lower compared to the non-autopsied group (Table 1). Therefore, the percentages of victims with a cardiac cause in this autopsied group were extrapolated to the non-autopsied group after adjusting for age and cardiac history.

Statistical methods

All data were entered into the SPSS-pc statistical program. Statistical significance for differences were tested by student t-test or Mann-Whitney-U test for continuous variables and chi-square test for proportions. A p-value < 0.05 was considered as statistically significant.

Table 1. Mean age, gender and previous cardiac history of victims with and without autopsy in the age categories 20-50 years and 50-75 years.

Age category 20 to 50 years	Autopsy N=33	No Autopsy N=21	P-value
Mean age (years)	41.5 ± 6.8	42.3 ± 7.1	ns
Men	20 (61%)	14 (67%)	ns
Previous cardiac history	10 (30%)	8 (38%)	ns
Age category 50 to 75 years	**Autopsy N=94**	**No Autopsy N=335**	**P-value**
Mean age (years)	63.7 ± 7.0	65.7 ± 6.1	<0.05
Men	74 (79%)	234 (70%)	ns
Previous cardiac history	43 (46%)	198 (59%)	<0.05

RESULTS

Of 127 autopsied victims, 94 (74%) were men. The mean age was 58 (± 12) years. A total of 87 (68.5%) were witnessed and 53 (42%) victims had a previous cardiac history. There were no significant differences in gender distribution (77% men vs 72% men) and mean age (59.7 (± 12) years vs 56.8 (± 12) years) between those with and those without a previous cardiac history.

1. Non cardiac causes

A non cardiac cause was found in 31/127 (24.4%) victims. In 3/53 (5.7%) with and in 28/74 (37.8%) without a cardiac history ($p < 0.001$).
As shown in Table 2, the most important non-cardiac causes were pulmonary embolism and hemorrhage from the aorta, each representing about 1/3 of the non-cardiac causes. The mean age of these latter victims was 56.4 (± 13.7) years.
One victim who was found dead was known with diabetes mellitus and another one suffered from epileptical disease. Because no other cause of death was found, it was assumed that they died because of hypoglycemia and epileptical insult respectively. In three cases (mean age 61 (± 8.7) years) the cause of sudden death remained unknown.
A non-cardiac cause was found in 18/87 (21%) witnessed victims and in 10/37 (27%) unwitnessed victims (ns). In 3 victims it was unknown whether they were witnessed.

Table 2. Causes of sudden death in victims with and without a previous cardiac history.

Causes of death	Previous cardiac history N = 53	No previous cardiac history N = 74
Cardiac	50 (94.3%)	46 (62.2%)
Non-cardiac:	3 (5.7%)	28 (37.8%)
Pulmonary embolism	1 (1.9%)	9 (12.1%)
Hemorrhage from the aorta	2 (3.8%)	8 (10.8%)
Pulmonary disease		4 (5.4%)
Intestinal bleeding		2 (2.7%)
Hypoglycemia		1 (1.4%)
Epileptical seizure		1 (1.4%)
No cause identified		3 (4.0%)

2. Cardiac causes

A cardiac cause was present in 96/127 (75.6%) victims. In two victims no myocardial infarction, significant narrowing of the coronary arteries or non-cardiac cause was found. One of them, a women of 23 years, was known with mitral valve prolapse and sick sinus syndrome. In the other victim, a women of 52 years, a pacemaker had previously been implanted because of complete AV-block. It was assumed that these victims had died suddenly because of a rhythm disorder. In 94/96 (98%) victims with a cardiac cause of sudden death, one or more significant stenosed coronary arteries and/or myocardial infarctions were found. Of these 48 (51%) had a previous cardiac history. There were no significant differences in gender distribution (38/48 men vs 34/46 men) and mean age (60.5 (± 10.5) years vs 57.3 (± 11.9) years) between victims with and without a cardiac history.

Findings in the myocardium and in the coronary arteries of coronary death victims

A heart weight of more than 400 grams was present in 79/94 (84%) of the sudden coronary death group and was more often found in victims with a previous cardiac history (45/48 (93.8%) vs 34/46 (73.9%): $p < 0.05$). Mean heart weight was 572 (± 126) grams in the subgroup with a previous cardiac history and 441 (± 81) grams in the other group ($p<0.001$).
In 88 of 94 (93.6%) sudden coronary death victims one or more coronary arteries were significantly (>75%) narrowed. Table 3 shows that in 23 (24.5%) cases one, in 32 (34%) victims two, in 30 (31.9%) three and in 3 (3.2%) cases 4 coronary arteries were significantly stenosed. In 6 (6.4%) victims a healed or recent MI was found in the myocardium without narrowing of more than 75% in one of the coronary arteries.

Comparison of the number of significantly narrowed coronary arteries between victims with and those without a previous cardiac history showed no significant differences (Table 3). Also the numbers of LM's, LAD's, RCA's and CX's which were significantly narrowed (>75%) were comparable in both groups (Table 3).
The LAD was totally occluded in 11/88 (12.5%) victims, the RCA in 10/88 (11.4%) victims and the CX in 4/88 (4.5%) victims.
One or more healed MI's were present in 51/94 (54.3%) of the total sudden coronary death group. Table 4 shows that a healed MI was present in 75% of the victims with a previous cardiac history but also in 33% of victims without a previous cardiac history.
A healed MI of the anterior wall of the left ventricle was more frequently found in victims with a previous cardiac history. There were no significant differences between the two groups in relation to other locations (Table 5).
A recent myocardial infarction was present in 55/94 (58.5%) of the total group of coronary death victims. It was found in 25/48 (52%) of the cases with and in 30/46 (65.2%) of the victims without a previous cardiac history (ns) (Table 4). Table 5 also shows that in both groups the recent MIs were equally distributed.
In 7/48 (14.6%) victims with and in 12/46 (26%) victims without a previous cardiac history no MI (old or recent) was found (ns) despite the presence of significantly stenosed coronary arteries.

Table 3. Distribution of number of significantly (>75%) narrowed coronary arteries in sudden coronary death victims with and without a previous cardiac history.

Number of vessels	Total number of victims N = 94	Previous cardiac history N = 48	No previous cardiac history N = 46	P-value
0	6 (6.4%)	2 (4.2%)	4 (8.7%)	
1	23 (24.5%)	11 (22.9%)	12 (26.1%)	
2	32 (34.0%)	16 (33.3%)	16 (34.8%)	ns
3	30 (31.9%)	18 (37.5%)	12 (26.1%)	
4	3 (3.2%)	1 (2.1%)	2 (4.3%)	
LM	9 (9.6%)	6 (12.5%)	3 (6.5%)	ns
LAD	65 (69.1%)	33 (68.8%)	32 (69.6%)	ns
RCA	62 (65.9%)	34 (70.8%)	28 (60.9%)	ns
CX	53 (56.4%)	28 (58.3%)	25 (54.3%)	ns

LM = left main, LAD = left anterior descending, RCA = right coronary artery, CX = circumflex artery

Table 4. Medical history in relation to autopsy findings in sudden coronary death victims.

Medical history	Total number of victims	Number of victims with a healed MI	Number of victims with a recent MI	Number of victims with significantly stenosed coronaries
No cardiac history	46	15 (33%)*	30 (65%)	42 (91%)
Cardiac history:	48	36 (75%)*	25 (52%)	46 (96%)
Coronary artery disease including previous MI	34	30	19	33
Stable/unstable angina pectoris without documented MI	6	2	2	6
Rhythm/conduction disturbances	4	1	2	4
LVH	2	2	1	1
Valve disease	2	1	1	2

* $p < 0.05$, MI = myocardial infarction, LVH = left ventricular hypertrophy

Table 5. Locations of healed and recent myocardial infarction in sudden coronary death victims with and without a previous cardiac history.

Location healed MI	Total number of victims N = 51	Previous cardiac history N = 36	No previous cardiac history N = 15	P-value
Anterior wall	18 (35%)	16 (44%)	2 (13%)	<0.05
Posterior wall	35 (69%)	25 (69%)	10 (67%)	ns
Lateral wall	16 (31%)	12 (33%)	4 (27%)	ns
Septum	13 (25%)	7 (19%)	6 (40%)	ns
Location Recent MI	N = 55	N=25	N=30	
Anterior wall	27 (49%)	15 (60%)	12 (40%)	ns
Posterior wall	42 (76%)	21 (84%)	21 (70%)	ns
Lateral wall	29 (53%)	14 (56%)	15 (50%)	ns
Septum	33 (60%)	17 (68%)	16 (53%)	ns

In some victims one, two or more healed/recent MIs were present in various places of the myocardium.

Relation between chest pain and recent myocardial infarction

In 64 of 94 (68%) coronary death victims sudden death was witnessed. In 12 witnessed victims it was unknown whether they had chest pain within the week before the event. Twenty eight of the remaining 52 (53.8%) witnessed victims complained of chest pain. A recent MI was found in 13/28 (46.4%) victims with chest pain and in 13/24 (54.2%) without chest pain.

3. Estimated yearly incidence of sudden cardiac death

In the age category 20-50 years, 33/54 victims were autopsied. A cardiac cause was found in 22/33 (66.6%) autopsied victims. It was estimated that the overall mean yearly incidence of sudden cardiac death in men and women aged 20 to 50 years was 1/10,000 inhabitants (((0.67 x 54)/4 years)/87,218). In the age category 50-75 years 94/429 victims were autopsied. A cardiac cause of death was present in 74/94 (79%) autopsied victims. After adjusting for age and cardiac history it was calculated that in total 274/335 (81.8%) of the non-autopsied group of victims between the age of 50 and 75 years had a cardiac cause of sudden death. It was then calculated that in the total age category (50-75 years) 74 + 274/429 (81.1%) victims had a cardiac cause of death. The estimated overall mean yearly incidence of sudden cardiac death in this group was 19/10,000/year (0.81 x 429 = 347.5/4 years = 87/45,543 inhabitants).
The estimated total mean yearly incidence of sudden cardiac death was 7/10,000 inhabitants between 20 and 75 years ((347.5 + 36)/483 = 79.5%; 384/4 years = 96/132,761).

DISCUSSION

In this study, cardiac and non-cardiac causes of sudden death were assessed by autopsy in more than one fourth of sudden death victims (witnessed and unwitnessed) who were prospectively included in a four year population based study in the Maastricht area. Information about the circumstances of the event and medical history of the victim was collected when possible. All autopsies were performed in the single hospital located in the Maastricht area.
In 3/4 of the autopsied sudden death cases a cardiac cause was present. This is in agreement with the results of Kuller (8) who demonstrated that the use of the 24 hours definition of sudden death reduces the proportion of all sudden natural cardiac deaths to 75%. The 24 hours definition of sudden death which was used in our study, made it possible to include not only witnessed but also all unwitnessed victims of sudden death.

In 62% of the victims without a previous cardiac history, sudden death was probably the first (acute) expression of heart disease. The number of non-cardiac deaths was significantly higher in the group without previous heart disease. In this group major bloodloss from the aorta and pulmonary embolism were the most important non-cardiac causes of sudden death. In three cases without a cardiac history, no cause could be identified. These patients may have died from a rhythm disturbance.
A non-cardiac cause was found in 33% of victims below the age of 50 years compared to 21% above this age. This is in agreement with Roberts (2) who reported that the younger the patient the higher the chance of a non-cardiac cause of sudden death.

Our data show that most sudden death victims had coronary artery disease. In 9 out of 10 sudden coronary death victims one or more coronaries were severely narrowed. Liberthson (9) found in 94% of the sudden cardiac death victims at least one coronary artery with a significant stenosis. Warnes (3) reported that in 84% of 70 out-of-hospital sudden coronary death victims at least 2 major arteries were more than 75% narrowed. As in the study of Warnes (3) our study showed no difference in the number of stenosed coronary arteries between victims with and without a cardiac history.
Cardiomegaly was often found in both groups of victims, but was more often present in victims with a cardiac history. Roberts (10) found in 74% of the out-of-hospital victims an increased heart weight and Baroldi (11) in 75% of 208 victims. In our study, the figures in victims with or without a cardiac history were 94% and 74% respectively. Cardiomegaly may be caused by cardiac dilatation and compensatory hypertrophy following a myocardial infarction. In our study a healed MI was present in 54% of the sudden coronary death victims which is comparable to the 50% reported by Friedman (12) while percentages of 40 to 70% have been reported by others (9,11,13,14). A healed MI was significantly more often present in victims with a previous cardiac history compared to those without. Davies (15) also demonstrated a strong relationship between a known history of ischemia and the presence of an old MI at autopsy. However in our study, a healed MI was also present in one third of the victims without a previous cardiac history which indicates that in these victims a previous MI was either silent or unrecognized.
Old anterior wall MIs were more often present in cases with a cardiac history which suggests that anterior wall MIs are more often (electrocardiographically) recognized than MIs occurring at other places in the left ventricle. Sudden death is frequently caused by ventricular fibrillation which can arise because of chronic myocardial changes such as hypertrophy and/or scarring (which predisposes the myocardium to have reentry as the initiating mechanism of ventricular fibrillation). It can also occur because of a new acute ischemic event (4).

In half of the witnessed victims who complained of chest pain a recent MI was found. It is possible that in the other half of these victims ischemia was less than four hours present which can not be diagnosed by the NBT staining. A recent MI was also found in more than half of those without chest pain. These victims may not have complained or in these victims silent ischemia could have played a role.

In epidemiologic studies on the incidence of sudden cardiac death, the cause of death is usually derived from the death certificate (16). However, when the diagnosis on the death certificate is compared to the cause determined by autopsy, a quarter to a third of the diagnoses had to be reclassified into other disease categories (17,18). Because our autopsied victims were prospectively included in a four years population based study in which every witnessed and unwitnessed case was registered, we estimated, based upon our autopsy data, the yearly number of sudden cardiac deaths. In the age category 50-75 years autopsy was performed in only 22% and this group was not entirely representative for all victims in this age group. The mean age and the number of victims with a previous cardiac history were significantly lower in the autopsied group compared with the non-autopsied group. This can be explained by the fact that permission for autopsy was probably more frequently given in young victims and in victims who had no cardiac history. Therefore in the age category 50-75 we adjusted for age and previous cardiac history when extrapolating the percentages of cardiac cause in the autopsied group to the non-autopsied group. Madsen (19) who also used the 24 hours definition of sudden death found that 77% of all victims who died suddenly outside hospital had a cardiac cause of death determined by autopsy and clinical data. This is comparable to our estimated total incidence rate of 79.5%.

In conclusion, in most autopsied victims a coronary cause of sudden death was present. A healed MI was more often present and the mean heart weight was higher in the group of sudden coronary death victims with a previous cardiac history. However a healed MI was found in more than one third of sudden coronary death victims who were unknown with a myocardial infarction. Interestingly, the number of significantly narrowed coronary arteries and recent MIs was not significant different between those with and those without a previous cardiac history. Our data suggest that in both groups sudden death was in most victims due to a recent ischemic event in the presence of severe coronary artery disease.

REFERENCES

1. Atkinson JB. Pathobiology of Sudden Death: coronary causes. Cardiovasc Pathol 1994;3:105-15.

2. Roberts WC. Sudden cardiac death: a diversity of causes with focus on atherosclerotic coronary artery disease. Am J Cardiol:1990;65:13b-19b.
3. Warnes CA, Roberts WC. Sudden coronary death: relation of amount and distribution of coronary narrowing at necropsy to previous symptoms of myocardial ischemia, left ventricular scarring and heart weight. Am J Cardiol 1984;54:65-73.
4. Davies MJ. Anatomic features in victims of sudden coronary death: coronary artery pathology. Circulation 1992;85:suppl I:I19-I24.
5. Farb A, Tang AL, Burke AP, Sessums L, Liang Y, Virmani R. Sudden coronary death: frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. Circulation 1995;92:1701-9.
6. Leach IH, Blundell JW, Rowley JM, Turner DR. Acute ischaemic lesions in death due to ischaemic heart disease: an autopsy study of 333 cases of out-of-hospital death. Eur Heart J 1995;16:1181-5.
7. Klein HH, Puschmann S, Schaper J and Schaper W. The mechanism of the tetrazolium reaction in identifying experimental myocardial infarction. Virchows Arch 1981;393:287-97.
8. Kuller L, Lilienfeld A, Fisher R. An epidemiological study of sudden and unexpected death in adults. Medicine 1967;46:341-61.
9. Liberthson RR, Nagel EL, Hirschman JC, et al. Pathophysiologic observations in prehospital ventricular fibrillation and sudden cardiacdeath. Circulation 1974;49:790-8.
10. Roberts WC, Potkin BN, Solus DE, Reddy SG. Mode of death, frequency of healed and acute myocardial infarction, number of major epicardial coronary arteries severely narrowed by atherosclerotic plaque, and heart weight in fatal atherosclerotic coronary artery disease: analysis of 889 patients studied at necropsy. J Am Coll Cardiol 1990;15:196-203.
11. Baroldi G, Falzi G, Mariani F. Sudden coronary death: a postmortem study in 208 selected cases compared to 97 "control" subjects. Am Heart J 1979, 98:20-31.
12. Friedman M, Manwaring JH, Rosenman RH, et al. Instantaneous and sudden deaths: clinical and pathological differentiation in coronary artery disease. JAMA 1973;225:1319-28.
13. Reichenbach DD, Moss NS, Meyer E. Pathology of the heart in sudden cardiac death. Am J Cardiol 1977;39:865-72.
14. Newman WP, Tracy RE, Strong JP, et al. Pathology of sudden cardiac death. Ann NY Acad Sci 1982;39:382-6.
15. Davies MJ, Bland JM, Hangartner JRW, Angelini A, Thomas AC. Factors influencing the presence or absence of acute coronary artery thrombi in sudden ischaemic death. Eur Heart J 1989;10:203-8.
16. Gillum RF. Sudden coronary death in the United States 1980-1985. Circulation 1989;79:756-65.
17. Thomas AC, Knapman PA, Krikler DM, Davies MJ. Community study of the causes of "natural" sudden death. Br Med J 1988;297:1453-6.
18. Cameron HM, McGoogan E. A prospective study of 1152 hospital autopsies: inaccuracies in death certification. J Pathol 1981;133:273-83.
19. Madsen JK. Ischaemic heart disease and prodromes of sudden cardiac death: is it possible to identify high risk groups for sudden cardiac death? Br Heart J 1985;54:27-32.

CHAPTER 11

Circumstances and Causes of Out-of-Hospital Cardiac Arrest in Sudden Death Survivors

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ABSTRACT

To study the circumstances and medical profile of out-of-hospital sudden cardiac arrest (SCA) victims in whom resuscitation was attempted by the ambulance service and to identify causes of SCA in survivors and factors that influence resuscitation success rate.

During a five year period (1991-1995) all cases of out-of-hospital SCA between the ages of 20 and 75 years and living in the Maastricht area in the Netherlands were studied. In all patients in whom resuscitation was attempted by the ambulance personnel, information was gathered about the circumstances of SCA, and the previous medical history of the patients. Causes of SCA in survivors were studied and logistic regression analysis was performed to identify factors associated with survival.

47 of 288 (16%) SCA victims in whom cardiopulmonary resuscitation (CPR) and advanced life support were applied were discharged alive from the hospital. Their mean age was 58 (± 11) years, 37 (79%) were men and 24 (51%) had a previous cardiac history. An acute myocardial infarction was diagnosed in 24 (51%) of survivors; in 7 with and in 17 without a previous cardiac history. Ventricular fibrillation (VF) or ventricular tachycardia (VT) as the first documented rhythm was significantly positively associated with survival (OR = 5.7, 95%CI:2.1-15.9). A time interval of less than 4 minutes between the moment of collapse and the start of resuscitation and an ambulance delay time of less than 8 minutes were significantly positively associated with survival (OR = 3.3 (95% CI: 1.3-8.6), and OR = 3.6 (95% CI: 1.3-10.5) respectively). A previous cardiac history was negatively associated with survival (OR = 0.46, (95%CI:0.21-0.98).

Acute myocardial infarction was found as the underlying mechanism of SCA in half of the survivors, especially in those without a previous cardiac history. Positively associated with success rate were basic CPR and/or advanced cardiac life support applied within 4 minutes, an ambulance delay time less than 8 minutes and VT or VF diagnosed by the paramedics.

INTRODUCTION

Unexpected cardiac arrest continues to be an important mode of death in the industrialized world. Unfortunately only a small proportion of all out-of-hospital sudden cardiac arrest (SCA) victims can survive to hospital discharge.
Study of survivors of SCA can give more insight into the circumstances and underlying mechanisms of SCA. Results of studies (1-4) on the etiology of SCA in survivors are contradictory. In the classical study from Seattle, only 20% of the survivors had a new transmural infarction (1). In contrast, a more recent study by Dickey et al. (3) reported that the etiology of ventricular fibrillation was an acute myocardial infarction (MI) in 69% of the patients who were successfully resuscitated. This was reason for us to study the causes of SCA in sudden death survivors and to investigate factors determining survival in SCA victims in whom resuscitation was attempted by the ambulance personnel in the Maastricht area.

METHODS

Study population

During a five year period (January 1st, 1991-December 31 st, 1995) 638 cases of unexpected out-of-hospital SCA occurred in people who were between the ages of 20 and 75 years and who lived in the region of Maastricht in the Netherlands. The area encloses 203 square kilometers and has approximately 182,000 inhabitants of whom around 133,000 (73%) are between the ages of 20 and 75 years. The area has one ambulance service with seven ambulances. All seven ambulances are equipped with defibrillators, material for intubation and oxygen administration and medication like adrenaline, atropine, lidocaine and procainamide. The ambulance service can be contacted 24 hours a day by calling 112. Each ambulance has one nurse and one driver. In case of SCA, always two ambulances are immediately directed to the scene.

Inclusion and exclusion criteria

Included in this study were all witnessed and unwitnessed victims of SCA living in the study region in whom resuscitation was attempted by the ambulance personnel. Excluded were patients with a circulatory arrest following a traumatic event or intoxication, or SCA occurring in the terminal phase of a chronic disease.

Data collection

In Maastricht all cases of out-of-hospital SCA were carefully collected. For that purpose, the ambulance service was contacted daily. In this study the data were analyzed from those SCA victims in whom resuscitation was attempted by the ambulance personnel.
From all patients, information was collected about age, gender, circumstances (place, time, complaints present before the event), whether and by whom the SCA was witnessed and whether or not resuscitation had already been initiated by a witness or bystander. This information was obtained from the ambulance personnel, the general practitioner and by interviewing witnesses or family members and the patient when possible. Information about the cardiac rhythm at the moment of arrival of the ambulance, the estimated time interval between the moment of collapse and the start of the resuscitation, the ambulance delay time (time between the moment of the emergency call and the moment of arrival) were obtained from a questionnaire which was filled out by the ambulance personnel immediately after the event.

All victims who were discharged alive from the hospital had been admitted to the coronary care unit of the department of Cardiology at the academic hospital in Maastricht. In all survivors serial electrocardiograms (ECG) and serial cardiac serum enzymes were determined. These included creatinine phosphokinase (CPK), serum glutamic-oxalacetic transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT) and lactic dehydrogenase (LDH). When CPK was increased, CK-MB fractions were also measured. Furthermore, in all but two patients echocardiograms were made during hospital stay. In 30 patients a coronary angiogram and in selected patients electrophysiological studies were performed. In all patients the cause of SCA was determined by consensus between the staff cardiologists of the department.
Information about the patients previous medical history, and morbidity was collected from the patient file of the general practitioner and from hospital records. Information about admission to a nursing home and mortality after discharge from the hospital was obtained by contacting the patients general practitioner.

Definitions

Sudden Cardiac Arrest was defined as unexpected, non traumatic loss of vital signs, such as consciousness, arterial pulse, blood pressure and respiration without preceding complaints or within 24 hours of the onset of complaints.

Witnessed SCA are arrests occurring in the presence of a bystander or emergency personnel. **Unwitnessed SCA** was defined as a SCA which occurred in a person being alone at the moment of SCA and found unconscious by a family member or neighbor, friend etc.
Acute myocardial infarction (acute MI) was diagnosed when the ECG showed the characteristic serial changes in Q waves and the ST-T segment. Furthermore a typical rise of all three enzymes (CPK > 240 U/l, LDH > 450 U/l and SGOT > 40 U/l) above the upper limit of normal was required and the CKMB% had to be greater than 5%.
Ischemic event or primary arrhythmic event. Included in this group were patients with ECG abnormalities suggesting ischemia rather than an acute MI (ST depression, changing polarity of T waves) or when their electrocardiogram did not show typical changes for MI or ischemia as described above. Furthermore the further clinical work-up confirmed ischemia or a primary arrhythmic event as the most likely cause and the CK-MB fraction was less than 5%.

Statistical methods

All data were analyzed using the SPSS-pc statistical program (5).
Statistical significance for differences have been tested by chi-square analysis for proportions and Mann-Whitney-U test for continuous variables. A p-value < 0.05 was considered as statistically significant. When proportions showed a trend over the years, the chi-square test for trend was calculated. Multiple logistic regression analysis was performed to analyze the relation between the **independent variables**: age (continuously), sex (women = reference category), presence of a previous cardiac history, resuscitation by witness or bystander, location of the event (outside home = reference category), estimated time between collapse and the start of resuscitation (continuously), the ambulance delay time (continuously) and the first documented rhythm (0 = asystole, bradycardia or other rhythm, 1 = ventricular tachycardia (VT) or ventricular fibrillation (VF)) and the **dependent variable** survival which was defined as discharged alive from the hospital. All variables were taken into consideration simultaneously. A second regression model was constructed with the same variables as mentioned above. However in this latter model, the time between collapse and the start of resuscitation and the ambulance delay time were included as two categorical variables. Odds ratios and their 95% confidence intervals (CI) were calculated.

Table 1. Baseline characteristics and circumstances of sudden cardiac arrest of survivors and non-survivors who were resuscitated by the ambulance personnel.

Variables	Survivors N=47		Non-survivors N=241		P-value
Gender					
men	37	(79%)	187	(78%)	
women	10	(21%)	54	(22%)	ns
Mean age (years)	58.1	(sd 11.3)	60.7	(sd 9.8)	ns
Cardiac history	24	(51%)	139	(58%)	ns
Event at home	24	(51%)	162	(67%)	0.05
Witnessed SCA	45	(96%)	212	(88%)	ns
Resuscitation by bystander	28	(60%)	102	(42%)	<0.05
First documented rhythm VT or VF	40	(85%)	123	(51%)	<0.001
Resuscitated within 4 minutes of the moment of collapse	34	(72%)	105	(44%)	<0.001
Ambulance delay time less than 8 minutes	41	(87%)	167	(69%)	<0.05

VT = ventricular tachycardia; VF = ventricular fibrillation

RESULTS

From January 1st 1991 until December 31st 1995, a total of 638 SCA victims were registered, with a yearly incidence of 129, 132, 134, 120 and 123 victims respectively. Thus yearly incidence did not change significantly over the years (9.8/10,000 inhabitants in 1991, 9.2/10,000 inhabitants in 1995). Age and gender distribution also did not change significantly over the years.
In 288/638 (45.1%) SCA victims, resuscitation was attempted by the ambulance personnel. In 47/288 (16.3%) victims resuscitation had been successful and these victims were discharged alive from the hospital.

Circumstances of sudden cardiac arrest in survivors

Table 1 shows baseline characteristics and circumstances of SCA of all survivors and non-survivors in whom resuscitation was attempted by the ambulance personnel.
Mean age of survivors was 58.1 (± 11.3) years and 37 (79%) were men. A previous cardiac history was present in 24 (51%). SCA occurred at home in 24/47 (51%) survivors. Seventeen (36.2%) were on the street or a public place, 2 (4.3%) were at work and in 3 (6.4%) SCA occurred during transport from

home to the ambulance and in one during transport (2.1%) to the hospital. SCA occurred during the night (between 24.00 pm and 6.00 am) and in the morning (between 6.00 am and 12.00 am) in respectively 5 (10.6%) and 9 (19.1%) of the survivors. In the afternoon (between 12.00 am and 18.00 pm) and during the evening (between 18.00 pm and 24.00 pm), SCA occurred in respectively 19 (40.4%) and 14 (29.8%) survivors. In 45/47 (95.7%) survivors a witness was present; in 19 a partner, in 6 another family member, in 11 a bystander, in 4 a nurse or physician and in 5 both a partner and an ambulance nurse. In two victims SCA was not witnessed. These patients were found unconscious by their partners who immediately called an ambulance. In a total of 28 (59.6%) survivors resuscitation was initiated by a witness or bystander before the ambulance arrived. In 14/28 (50%) cases resuscitation attempt was started by a nurse or physician. The mean estimated time interval between the moment of collapse and the start of the resuscitation attempt was 2.7 ± 3 minutes while the ambulance delay time was 5.9 ± 2.6 minutes. The first documented rhythm by the ambulance personnel was VF in 38 (80.9%), VT in 2 (4.3%), bradycardia in 5 (10.6%) and asystole in 2 (4.3%) survivors.

Factors that influence resuscitation success rate

The logistic regression model (Table 2) shows that of all variables, VT/VF as the first documented rhythm by the ambulance personnel was significantly positively associated with survival in resuscitated victims. The presence of a previous cardiac history, an increasing time between the moment of collapse and the start of resuscitation were significantly negatively associated with survival.
A time delay between the moment of collapse and the start of resuscitation of less than 4 minutes and an ambulance delay time of less than 8 minutes showed to be significantly positively associated with survival (OR = 3.3 (95% CI: 1.3-8.6), and OR = 3.6 (95% CI: 1.3-10.5) respectively).

Figure 1 shows that the number of resuscitation attempts did not change significantly over the years. The number of SCA victims who survived more than 24 hours after successful resuscitation and were admitted to the coronary care unit of the hospital increased from 20% in 1991 to 38% in 1995 ($p<0.05$). The number of SCA victims who were discharged alive from the hospital increased from 12% in 1991 to 25% in 1995 ($p<0.05$) (Fig. 2).
Table 3. shows that in the 5 year period there has been no change in baseline characteristics, place of the event, the number of bystander resuscitations, bystander success rate, time interval between the moment of collapse and the start of resuscitation and in ambulance delay time. There is also no difference in the number of victims found in VT/VF and in the number of SCA victims witnessed by the ambulance personnel over the years.

Table 2. Results of multiple logistic regression analysis, with survival as the dependent variable.

Variables	Odds Ratios (95% CI)	
Gender: (men vs women)	1.39	(0.54-3.62)
Age (years)	0.97	(0.93-1.00)
Previous cardiac history (yes/no)	0.46	(0.21-0.98)
Location of the event: (at home/not at home)	0.84	(0.38-1.87)
Resuscitation started by a bystander or witness (yes/no)	1.45	(0.62-3.36)
Time interval between the moment of collapse and the start of resuscitation (minutes)	0.85	(0.75-0.96)
Ambulance delay time (minutes)	0.89	(0.78-1.00)
First documented rhythm: (VT/VF vs other rhythm)	5.72	(2.10-15.96)

CI = confidence intervals, VT=ventricular tachycardia, VF = Ventricular fibrillation

Table 3. Comparison of factors influencing resuscitation success rates 1991-1995.

Variable	1991 N = 51	1992 N = 60	1993 N = 57	1994 N = 59	1995 N = 61	p-value
Men	43 (84%)	47 (78%)	44 (77%)	47 (80%)	43 (70%)	ns
Cardiac history	35 (69%)	29 (48%)	31 (54%)	38 (64%)	30 (49%)	ns
Age						
20-40 years	2	0	3	4	1	
41-60 years	22	23	18	25	28	
61-75 years	27	37	36	30	32	ns
Place: at home	27 (53%)	41 (68%)	35 (61%)	44 (75%)	39 (64%)	ns
Rhythm VT/VF	28 (55%)	34 (57%)	32 (56%)	34 (58%)	35 (57%)	ns
Time interval col-res < 4 min	24 (47%)	27 (45%)	29 (51%)	29 (49%)	30 (49%)	ns
Ambulance delay time < 8 min	39 (76%)	47 (78%)	38 (67%)	41 (69%)	43 (70%)	ns
Bystander resuscitation	24 (47%)	19 (32%)	32 (56%)	30 (51%)	25 (41%)	ns
Success rate bystander resuscitation	4/24 (17%)	4/19 (21%)	5/32 (16%)	7/30 (23%)	8/25 (32%)	ns
Witnessed by amb. nurse	3 (6%)	7 (12%)	2 (4%)	5 (8%)	9 (15%)	ns

VT / VF = ventricular tachycardia /ventricular fibrillation; col-res = collapse - resuscitation attempt; < 4 min = less than 4 minutes; < 8 min = less than 8 minutes; amb. = ambulance nurse

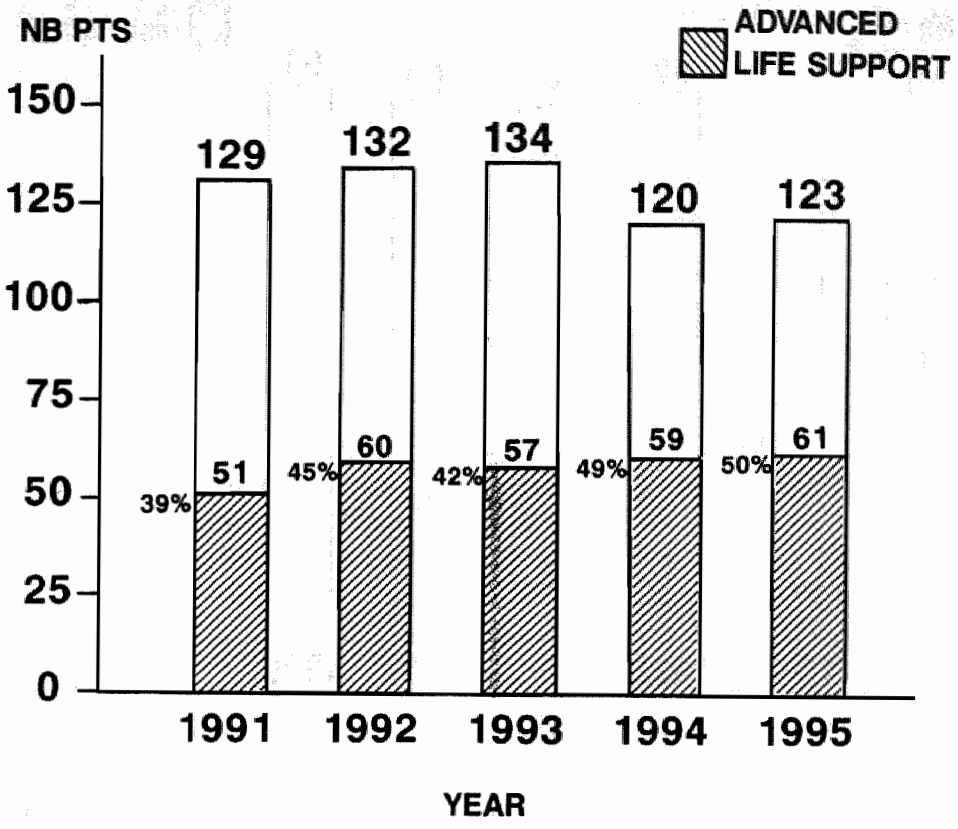

Figure 1. Yearly number of SCA victims in whom advanced life support was applied.

Causes of sudden cardiac arrest in survivors

An acute MI was diagnosed in 24/47 (51%) survivors. It was diagnosed in 7/22 (32%) with a previous cardiac history and in 17/25 (68%) without a previous cardiac history ($p<0.05$). Of 24 patients with an acute MI, the location was anterior in 10 (41.6%) patients, posterior in 9 (37.5%) patients and inferior in 4 (16.7%). In one patient the location of the infarct was not traceable because of multiple old infarctions.

An ischemic event or a primary arrhythmic event caused by an old MI was most probably the cause of SCA in 19 victims. In four other survivors the causes of SCA were respectively pulmonary embolism, complete AV-block, ventricular tachycardia in a patient with severe mitral valve disease and ventricular fibrillation as the first expression of the WPW syndrome.

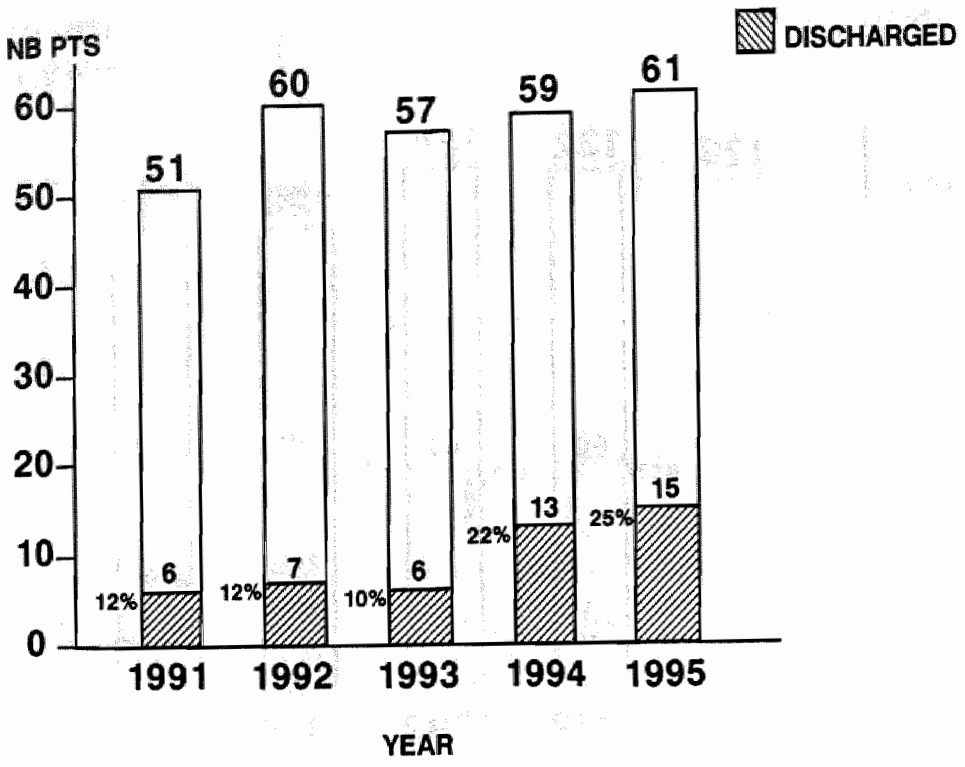

Figure 2. Yearly number of SCA victims in whom advanced life support was applied and the number of patients who were discharged alive from the hospital.

Diagnostic work-up and interventions during hospital admission

In all but two survivors an echocardiogram was made after the event. In 11 of 21 survivors with and in 1 of 24 survivors without a previous cardiac history the left ventricular ejection fraction (LVEF) was less than 40%.
In 20/24 survivors with an acute MI a coronary angiogram was made. One significantly narrowed vessel (> 50% narrowed) was present in 6 survivors, two vessel disease in 5 and three vessel disease in 9 survivors. In 12 survivors percutaneous transluminal coronary angioplasty was performed and in 2 coronary artery bypass grafting was done while 4 patients received thrombolytic therapy and 6 survivors received heparin and nitroglycerine.
In 14/19 survivors with an ischemic or primary arrhythmic event, a coronary angiogram was made. In 2 patients 1 vessel was significantly narrowed, in 6 patients 2 vessels and in another 6 patients 3 vessels. In 7 patients a defibrillator was implanted.

Complaints in relation to causes of sudden cardiac arrest

Of 24 survivors in whom an acute MI was diagnosed, 19 patients suffered chest pain before the event. In 13 chest pain started within one hour before SCA. In the other 6 patients chest pain had been present for more than 1 hour before SCA.
In 17/23 survivors in whom no acute MI was diagnosed, no complaints were present before SCA. In 4 survivors severe dyspnea was present within one hour before the event, while in 2 victims it was unknown whether they had complaints.

Follow up

Of the 47 survivors, 4 men and 2 women (12.8%) were admitted to a nursing home after hospital discharge because of irreversible hypoxic encephalopathy. Mean age was 63 (± 11) years and 2 of these patients had a previous cardiac history. In 3 patients an acute MI, in 2 an ischemic event and in 1 patient a primary arrhythmic event had been diagnosed.
Forty three of the 47 patients (91.5%) survived for more than one year after the event. All four patients who died within one year after the event were men and in three of them an acute MI had been diagnosed. They had not been admitted to a nursing home. Three patients died suddenly, one because of pulmonary embolism. One patient died during peripheral vascular surgery.

DISCUSSION

In this study we describe circumstances and causes of out-of-hospital SCA in patients in whom resuscitation was attempted by the ambulance personnel and who survived to hospital discharge. All patients were included in a five year prospective registry of out-of-hospital cardiac arrest in the Maastricht area in the Netherlands and were admitted to the same hospital. In more than half of the survivors, SCA occurred during day time and half of all patients were not at home. These two circumstances may enhance the chance of being witnessed and being resuscitated immediately or within a few minutes. As shown by our and other studies, an increasing ambulance delay time (more than 8 minutes) and an increasing estimated time interval between the moment of collapse and the start of resuscitation (more than 4 minutes) were important independent factors which are negatively associated with survival (6-9). Also increasing age was negatively associated with survival, but this was not significant. Bystander resuscitation was significantly positively associated with survival (OR 2.2, $p = 0.04$) when the time between collapse and the start of resuscitation was excluded from the

logistic regression model. An other important variable in this respect is VT or VF as the first documented rhythm. As in other studies (2,10-13), most of our survivors had VF as the first documented rhythm which was positively associated with survival in those in whom resuscitation was attempted. A previous cardiac history was significantly negatively associated with survival. This may be explained by the fact that in those with a previous cardiac history cardiac function was already diminished before the event. Half of the survivors with a previous cardiac history had a LVEF of less than 40% after the event while this was the case in only 1 of those without a previous cardiac history. Hallstrom et al suggested that comorbidity was an important predictor for survival (14).
The increase in resuscitation success rate over the years can be explained by many factors. Possible factors which may have been of influence are: 1) That since the end of 1993, all ambulances are equipped with portable defibrillators and portable apparature for monitoring rhythm and blood saturation. 2) That at that time, all nurses and drivers had received a professional training in resuscitation.

Cardiac causes of SCA can be classified as ischemic and non-ischemic. Different manifestations of ischemic heart disease include: acute MI, acute myocardial ischemia and a healed MI that serves as a substrate for VT deteriorating into VF (15). In all but one survivor the cause of SCA was cardiac. Of the patients who had a coronary angiogram during hospital stay nearly 76.5% showed to have two or three vessel disease. Myerburg (10) reported that 81% of the patients who had significant coronary artery lesions had two or three vessel disease.
In half of all patients an acute MI was diagnosed. Early studies have reported that an acute MI was diagnosed in only a minority of victims who were successfully resuscitated (1, 2,10). In a study from Seattle, only 20% of the survivors had a new transmural infarction (1). The etiology of SCA was determined in 109 survivors studied by Myerburg et. al. (2,10). In 86 (79%) patients coronary artery disease was present and in 31 (28%) patients acute myocardial necrosis was documented. In contrast, Dickey et al. (3) reported that the etiology of VF was an acute MI in 69% of the patients who were successfully resuscitated (including those who died during hospital admission). Goldstein (4) reported that in 142 SCA patients with coronary heart disease who were resuscitated and discharged from the hospital, the cardiac arrest was classified as being secondary to an acute MI in 44%, an ischemic event in 34% and a primary arrhythmic event in 22% . The majority of these patients (77%) had a history of cardiac disease. These differences in the number of survivors with an acute MI, may be explained by the use of different criteria for acute MI (only transmural MIs) or by differences in baseline characteristics of survival groups. The higher number of patients in whom an acute MI was diagnosed in our study, may be explained by the fact

that half of the survivors had no previous cardiac history. An acute MI was diagnosed in 68% of these victims compared to only in 32% of the patients known with a cardiac disease.

In this study, the determination of the mechanisms of SCA was based on only a small fraction of all SCA victims. However autopsy on SCA victims who were also included in the four years registry showed comparable results. In 96 of 127 autopsied SCA victims the cause of sudden death was cardiac. The underlying mechanism was coronary artery disease in 94/96 (98%) victims (mean age 58.9 (± 11.2) years, men 72 (77%), previous cardiac history 48 (51%)). This latter group was comparable with the survivors who had coronary artery disease according to mean age, gender and previous cardiac history. At autopsy a recent MI was found in 58.5% victims; in 52% of the victims with and in 65% of the victims without a previous cardiac history.

It is however not possible to determine how many acute MIs were the initiating factor and how many MIs were a consequence of SCA (2). However in the majority of our survivors with an acute MI, chest pain was reported before SCA. In more than two third of them, VF developed within one hour of the onset of chest pain.

As mentioned above, 24% of the autopsied group had a non-cardiac cause. Among the survivors there was only 1 patient with a non-cardiac cause. This suggests that a non-cardiac cause of SCA is negatively associated with survival.

In our patient group, one year mortality after discharge was 8.5% which is lower compared to one year mortality rates reported by others (11,12,16,17). One year mortality in those studies were 24%, 20% and 21% respectively. As reported by Schaeffer and Cobb (18), most of the recurrent SCA within two years after SCA occurred in those patients in whom no acute transmural MI was diagnosed. The expected overall one year recurrent cardiac arrest in these survivors of out-of-hospital SCA on uncontrolled long-term management was 30% and the two year recurrence rate 45% (10). The lower one year mortality rate in our study may be explained by the fact that in half of the survivors an acute MI was diagnosed and secondly by the intensive treatment and long-term management of those in whom an ischemic or primary arrhythmic event was diagnosed. In seven patients a defibrillator was implanted which has shown to be associated with a reduction in cardiac mortality (19).

In summary, in 51% of all SCA survivors an acute myocardial infarction was diagnosed as the underlying mechanism of SCA. Complaints of chest pain before the event were mainly present in patients in whom a diagnosis of acute MI was made. SCA occurred immediately or within one hour of the onset of complaints in 87% of the survivors.

Findings in survivors suggest that an acute myocardial infarction is often the cause of SCA, especially in those without a previous cardiac history. This stresses the importance of educating the general population to go

immediately to an area where advanced life support can be provided when symptoms suggest an acute myocardial infarction. The correct surrounding is not only important for early thrombolytic treatment but also for successful resuscitation if a lethal arrhythmia supervenes.

REFERENCES

1. Baum RS, Alvarez H, Cobb LA. Survival after resuscitation from out-of-hospital ventricular fibrillation. Circulation 1974;50:1231-5.
2. Myerburg RJ, Kessler KM, Zamann L, et al. Survivors of prehospital cardiac arrest. JAMA 1982;247:1485-90.
3. Dickey W, Adgey AAJ. Mortality within hospital after resuscitation from ventricular fibrillation outside hospital. Br Heart J 1992;67:334-8.
4. Goldstein S, Landis JR, Leighton R, et al. Characteristics of the resuscitated out-of-hospital cardiac arrest victims with coronary heart disease. Circulation 1981;64:977-84.
5. Norusis MJ. Base Manual. SPSS Inc. Chicago, Illinois (USA) 1988.
6. Becker LB, Ostrander MP, Barnett J, Kondos GT. Outcome of CPR in a large metropolitan area: were are the survivors? Ann Emerg Med 1991;20:355-61.
7. Eitel DR, Walton SL, Guenci AD, Hess DN, Sabulsky NK. Out-of-hospital cardiac arrest: a six year experience in a suburban-rural system. Ann Emerg Med 1988;17:808-12.
8. Wilcox-Gok VL. Survival from out-of-hospital cardiac arrest: a multivariate analysis. Crit Med Care 1991;29:104-14.
9. Eisenberg MS, Hadas E, Nuri I, et al. Sudden cardiac arrest in Israel: factors associated with successful resuscitation. Am J Emerg Med 1988:6:319-23.
10. Myerburg RJ, Conde CA, Sung RJ, et al. Clinical, electrophysiologic and hemodynamic profile of patients resuscitated from prehospital cardiac arrest. Am J Med 1980:68;568-76.
11. Goldstein S, Landis R, Leighton R. Predictive survival models for resuscitated victims of out-of-hospital cardiac arrest with coronary heart disease. Circulation 1985;71:873-80.
12. Herlitz J, Ekstrom L, Wennerblom B, Axelsson A, Bang A, Holmberg S. Prognosis among survivors of prehospital cardiac arrest. Ann Emerg Med 1995;25:58-63.
13. Stueven HA, Waite EM, Troiano P, Mateer JK. Prehospital cardiac arrest: a critical analysis of factors affecting survival. Resuscitation 1989;17:251-9.
14. Hallstrom AP, Cobb LA, Hui Yu B. Influence of comorbidity on the outcome of patients treated for out-of-hospital ventricular fibrillation. Circulation 1996;93:2019-22.
15. Waldo AL, Biblo LA, Carlson MD. General evaluation of out-of-hospital sudden cardiac death survivors. Circulation 1992;85:I103-I106.
16. Eisenberg MS, Hallstrom A, Bergner L. Longterm survival after out-of-hospital cardiac arrest. N Engl J Med 1982;306:1340-43.
17. Kimman GP, Ivens EM, Hartman JA, Hart HN, Simoons ML. Long-term survival after successful out-of-hospital resuscitation. Resuscitation 1994;28:227-32.
18. Schaeffer WA, Cobb LA. Recurrent ventricular fibrillation and modes of death in survivors of out-of-hospital ventricular fibrillation. N Engl J Med 1974;293:259-62.
19. Powell AC, Fucks T, Finkelstein DM, et al. Influence of implantable cardioverter - defibrillators on the long-term prognosis of survivors of out-of-hospital cardiac arrest. Circulation 1993;88:1083-92.

CHAPTER 12

General Discussion

Part I

Although mortality figures early and late after acute myocardial infarction (MI) and unstable angina pectoris (UAP) have decreased during the past decades, coronary heart disease (CHD) is still the leading cause of death in the western world and has a major impact on health costs. To make correct decisions about the incorporation, expansion or limitation of preventive and curative measures it is important to study the causes of the decrease in mortality (1). A decrease in *mortality* can be achieved by a decreased *incidence* and/or by decreased *case fatality* rates.

A decline in *incidence* of CHD may be related to primary preventive measures, such as changes in life-style, drugs to control hypertension, and as recently shown, hypercholesterolemia and possibly platelet aggregation. Changes in life-style are reflected in decreased smoking habits, increased physical fitness and diet changes. How much this contributes to a decrease in mortality is still a matter of investigation (2). A recent study shows that only 25% of the decline in CHD mortality can be explained by primary prevention (3).

We found a similar incidence of acute MI and UAP during more than a decade. This may be explained by a decrease in the young and an increase in the older population of the region of Maastricht.

The decrease in mortality may also be related to lower *case fatality* rates, largely due to improvement in early management, risk stratification, more accurate diagnostic techniques, and more effective therapies. It is well recognized that the use of thrombolytic therapy and balloon angioplasty in the early hours of MI leads to myocardial salvage and a better outcome in-hospital and after discharge. Certain clinical features such as the extent and location of MI, severe reduction in left ventricular function, recurrent ischemia or ventricular arrhythmias and patient characteristics apparent during the early period of MI and UAP indicate an increased risk for death. This resulted in emphasis on risk stratification in the early hours after MI and a more aggressive approach in the high risk group. Furthermore the improved outcome after MI is related to secondary preventive measures using drugs (e.g., beta-blockers, aspirin, ACE-inhibitors) and the advent of better diagnostic techniques to detect recurrent ischemia or depressed left ventricular function.

The change in age of the patients will significantly influence mortality figures. It is expected in general and observed in the Maastricht population that the incidence of MI increases in the older age group. Through better treatment of severe non-cardiac diseases future patients with CHD will even be older and possibly the prevalence of risk factors such as diabetes or hypertension will increase with age. However, the question arises whether the occurrence of risk factors at an older age has the same effect as exposure

to a harmful level of a risk factor at a young age. This is still a matter of investigation (4).
The relative risks of CHD associated with the standard risk factors weaken with increasing age, perhaps because of selective survival and competing risk. This has been demonstrated for smoking where the increased relative risk of CHD caused by cigarette smoking decreased in older age groups, perhaps because of selective loss of smokers due to premature death of other causes such as cancer or peripheral vascular disease (5). Finally elderly people may be more susceptible to the side effects of interventions.

Early and late mortality

Mortality outside the hospital occurs before any treatment can be given. It can only be reduced when all the components of the 'chain of survival' can be applied on time during the resuscitation attempt (6). Another category of mortality is that occurring within the first 24h of admission, reflecting extensive or complicated MI, for which effective treatment is not possible. These two categories comprise a great number of CHD deaths.
Thus it should be realized that the impact of in-hospital treatment on overall mortality is relatively small. To reduce mortality from MI and UAP before admission to the hospital it is of importance to inform the public and health workers how to handle in the case of acute chest pain in order to reduce unnecessary delay before admission. In this study we observed a significant reduction in delay time between the beginning of chest pain and admission to the hospital over the years. Furthermore an appropriate service should be present in the community to reach and treat SCA victims as discussed in part II of this thesis. Finally it should be realized that although sudden cardiac death outside the hospital contributes importantly to the total acute mortality, only half of these patients can be recognized as possible candidates before the event. Figure 1 shows that in 1995 51% of SCA victims had no previous cardiac history. Only a minority of the patients with a previous history had a MI in the previous year. This shows that the incidence of sudden death is low in the first year after MI.
In-hospital mortality from acute MI and UAP is nowadays around 10% and 1% respectively. Reports on selected patients included in drug trials show a lower mortality in acute MI. It is possible that the lowest limit of in-hospital mortality has been reached and that new achievements will have only minor effect on mortality figures. Patients who die in-hospital are old and they frequently have a history of previous infarction with a diminished left ventricular function. Figure 2 shows these data for the 1994 patients indicating an in-hospital mortality of 38% in the small group of those with a left ventricular ejection fraction less than 30%.

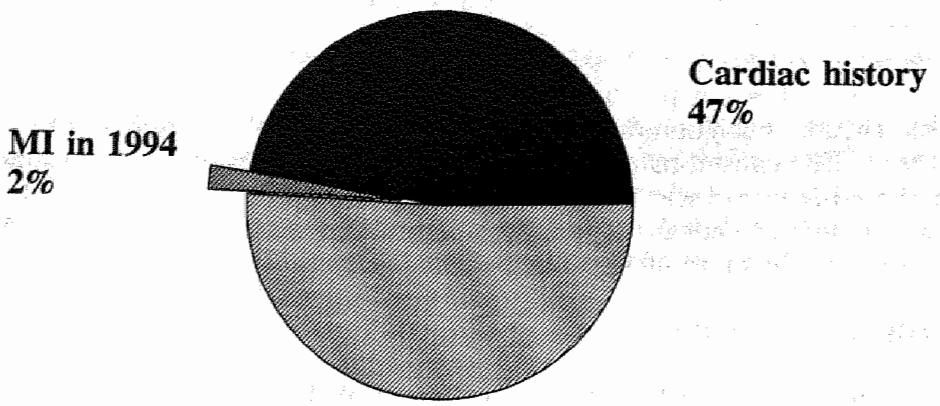

Figure 1. Previous history in SCA victims in 1995

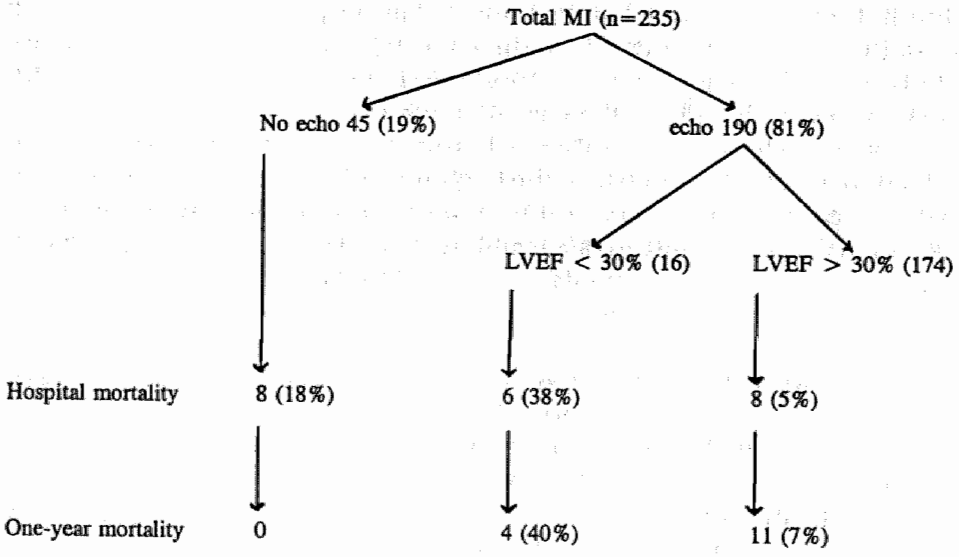

Figure 2. Mortality in patients admitted with myocardial infarction in 1994 with an ejection fraction below and above 30%.

Because the survivors of myocardial infarction have an increased risk of recurrent ischemia, pump failure and arrhythmias, it is not surprising that a declining mortality rate in the acute phase has been accompanied by a marked increase in interventions and drug treatment in recent years.
Numerous treatment strategies such as thrombolytic therapy, balloon angioplasty and different drugs such as ACE-inhibitors have been introduced and evaluated and studies are still ongoing. In selected patients randomized placebo controlled trials were performed to compare the effects of new treatment modalities on different end-points. These studies are, however performed in selected patient populations. Although the information gained is helpful in assessing the value of the intervention, the information on changes in prognosis is not readily applicable to the general population with MI. Some patients may not receive any new treatment, whereas others may receive more than one, or may receive treatment modified from the study treatment.

Late mortality can be influenced by secondary preventive measures and by identifying and more aggressive treatment of the patient at risk following the initial phase. The early detection of recurrent ischemia has been particularly successful, and has led to appropriate strategies to prevent reinfarction. Parallel to a decrease in mortality are variables such as age, a longer cardiac history and co-morbidity that might increase late mortality from CHD.

Comparing prognosis of patients after an acute ischemic syndrome with data from previous years has been done to study trends in mortality and morbidity over time. It should be realized that comparing mortality and morbidity data of one year with previously published data has some limitations. There can be a change in diagnostic procedures and accuracy leading to inclusion of different patients in the years. Also the attitude of general practitioners and hospital doctors to refer and admit patients can change over the years and possibly a change of the awareness of the public and health workers how to act in case of acute chest pain might lead to changes in the population admitted with an acute ischemic syndrome. Another factor that may influence comparability of patients admitted in different years is the modification of the natural history. Patients admitted in recent years are older and have more often a history of prior interventions, also they are receiving more drugs for secondary prevention.
Finally it should be realized that a possible bias in studies comparing patients admitted in different years is the increased detection of less severe disease resulting in an increased incidence and a lower case fatality rate in more recent years (7). In this study there was no change in the methods of inclusion and the diagnostic tests for MI and UAP remained constant over the years.

This study has shown that in-hospital mortality and long-term mortality after MI decreased over the years. This decrease was caused by changes in medical treatment and the use of new surgical and catheter interventions. The incidence of MI did not change because of the increase in the number of older patients with a first MI. It is therefore important to focus especially on the treatment of the older MI patient. To reduce the incidence of MI in the older age group, more attention should be given to the identification and treatment of CHD risk factors in this group of the population (4).

To gain insight into the effectiveness of changing treatment strategies on prognosis in the general MI population, studies should be performed in several representative institutions within one country and, if possible, within several other countries and repeated at different time periods. The population studied by these institutions should reflect the general population within the community. No age limit should be enforced, because, since the ageing population is rapidly increasing, this group is likely to be under-treated.
Unstable angina patients should also be included. At the time of admission to the hospital important treatment decisions are made, but the final diagnosis (acute MI or unstable angina) may not yet be clear, because cardiac enzymes do not immediately reflect loss of cardiac tissue. Diagnostic work-up should include assessment of morbidity, quality of life and mortality (causes of cardiac and non-cardiac death, preferably confirmed by autopsy). Only multicenter studies, repeated at regular intervals could provide accurate information on changes in prognosis of acute MI, the factors leading to these changes, and their economic implications.

Part II

Sudden cardiac arrest (SCA) is a common cause of death and therefore continues to be a major health problem in the Netherlands and other industrialized countries. In general, it is a most dramatic event often occurring in people who are in the prime of their lives.
The Council of Health on the epidemiology and prevention of CHD in the Netherlands reported in 1984 that registration networks are needed to study the incidence, prevalence, morbidity and mortality of CHD, the effect of interventions and to identify high risk groups (1). Our network to register both witnessed and unwitnessed SCA victims was the first in the Netherlands and started in 1991 in the region of Maastricht. This region is a well defined area with a single hospital and one emergency medical service (EMS). Thanks to the cooperation of all EMS workers and general practitioners, all witnessed and unwitnessed SCA victims were registered prospectively. This

made it possible to get a representative figure on the incidence and survival rates of SCA in the Maastricht population.

The incidence of SCA which was determined in our study is difficult to compare with reported figures of studies performed in other communities. Many of these studies based their incidence rates on the number of people who were resuscitated by the EMS (8). Furthermore differences in reported incidence rates can also be explained by the use of different definitions of SCA. The use of the '1, 6 or 24 hours' definition of SCA will lead to different numbers of SCA. Recently many studies on SCA used the '1 hour' definition. Using this latter definition has the consequence that victims who are in pain for more than one hour, but who do not complain are also included while most unwitnessed victims will not be included. In this study we used the 24 hours definition to include also victims who were unwitnessed but who died most probably suddenly. However, the use of this latter definition has as its consequence that victims with a non-cardiac cause of sudden death are also included.

Almost half of the SCA victims had no previous cardiac history and in the majority of these, SCA was probably the first acute expression of heart disease. Studies have tried to identify people in the general population without overt CHD who are at high risk for sudden cardiac death. However this has shown to be difficult mainly because of the fact that most risk factors who are predictive for coronary artery disease are also predictive for sudden coronary death. This implicates that prevention has to be focused on preventing the occurrence and progression of coronary artery disease by identifying and controlling risk factors in the population not known with heart disease (9).
The other half of the victims were already known with heart disease most often coronary artery disease. As shown by this and other studies, patients with a previous MI have a higher risk of dying suddenly compared to those without a MI. Therefore many attempts have been made in making a risk profile for SCA in survivors of MI at the time of discharge from the hospital. However the current methods of risk stratification for sudden cardiac death allow to identify only a small fraction of such patients (10).
Patients who are treated for a symptomatic ventricular tachy-arrhythmia or ventricular fibrillation in the setting of a healed MI have a high risk for dying suddenly in the future. These patients are less difficult to recognize and implantation of a defibrillator is a successful and well accepted therapy. However, the problem is much more difficult in MI survivors who do not suffer from spontaneous ventricular arrhythmias (10).
In the last decade many tests have been introduced to identify patients who are at high risk for SCA after MI (Table 1) (11-15).

Table 1. Risk stratification for sudden death

Coronary perfusion:	Coronary angiography
	Exercise testing (+ nuclear)
	Holter recording
Pump function:	Functional class
	LVEF
	Exercise duration
Arrhythmias:	Signal averaged ECG
	Holter
	QT interval duration and disparity
	Exercise testing
	PES
Neurohumoral:	Heart rate variability
	Baroreflex sensitivity
Psychosocial:	Depression

ECG = electrocardiogram, LVEF = left ventricular ejection fraction, PES = programmed electrical stimulation.

Left ventricular dysfunction and ventricular arrhythmias are both significantly associated with sudden cardiac death (16). However it is emphasized that these tests alone or in combination have a high negative but a low positive predictive value (10). This means that of those patients who have a positive test result only a small percentage will die suddenly. However because of the relatively low incidence of sudden death in patients discharged after MI, the absolute number of deaths in those with a positive test result may be the same or even less than the absolute number of deaths in those with a negative test result. This would not be a problem when sudden death in all MI patients could be prevented adequately by low cost treatments with no side effects, but unfortunately no such treatment is available. The Cardiac Arrhythmia Suppression Trial (17) (CAST) experience indicates that after a myocardial infarction, some antiarrhythmic drugs thought to prevent sudden death will actually increase the number of patients dying suddenly. Only beta-blocking drugs have been shown to be (moderately) effective (18) and therefore CHD patients should receive such a drug lifelong unless there is a contraindication to its use.

It is difficult to identify the post MI patient who did not suffer from a life threatening ventricular arrhythmia but who is at high risk for sudden cardiac death and who might benefit from an expensive prophylactic treatment such as implantation of a defibrillator. Because of the low positive predictive value of diagnostic tests, defibrillators would be implanted in many patients in whom no life-threatening episodes will occur. The current methods of risk stratification in MI patients will therefore result in only a minor reduction in the total number of sudden deaths outside hospital.

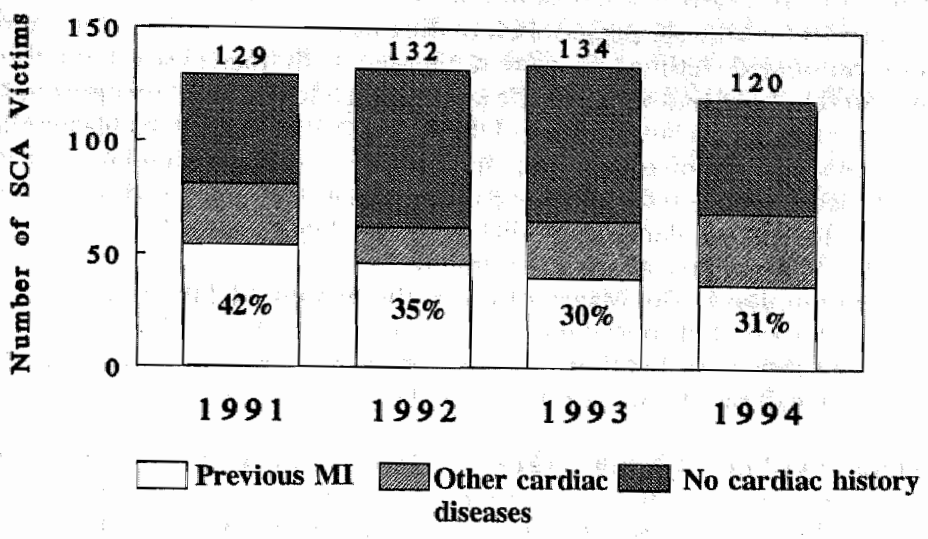

Figure 3. Previous medical history of SCA victims.

In MI patients the progression of coronary artery disease should be delayed by controlling risk factors and life-style factors. Furthermore prevention should be focused on the identification of transient pathophysiological events that initiate fatal arrhythmias (19). The appropriate steps should be taken to optimize myocardial perfusion and pump function.
In our study the total number of SCA victims with a previous MI decreased from 43% in 1991 to 31% in 1994 (Figure 3). This decrease may be explained by a decrease in yearly incidence of MI or by the positive effect of secondary prevention after MI. A recent study by Hunink et al, shows that most of the decline in CHD mortality in the US between 1980 and 1990 could be explained by improvements in the management of patients with diagnosed CHD through risk factor reduction and improvement in treatment (3). However, in our study, the total incidence of SCA did not decrease significantly. This suggests that an even larger proportion of the SCA victims cannot be identified before the fatal event and that other strategies have to be considered (10,20).

The presence of one hospital in the region made it possible to get optimal data on less selected groups of SCA victims who were autopsied and of those who survived to hospital discharge. In most victims, especially those without a previous cardiac history, the underlying cause of sudden cardiac death was a recent MI as shown by autopsy in non-survivors and by diagnostic

evaluation in survivors. In most of the latter victims typical symptoms and complaints for MI were present before the unexpected event. Furthermore, in the autopsied victims who were not known with heart disease one third appeared to have had an MI in the past which had not been recognized by the patient or physician. Because of these observations, it seems reasonable to give more attention to educate, especially the population not known with heart disease, how to recognize symptoms of an acute MI and to instruct them to call an ambulance immediately so that they, in case of SCA, can have advanced life support as soon as possible.
Our finding that in the Maastricht area the hospital delay time (the time between the onset of chest pain and admission to the hospital) is decreasing (chapter 3), suggests that there is a growing awareness among laymen of the importance of rapid transport to hospital when MI is suspected.

In those in whom SCA still occurs outside the hospital, the best chance to survive is to minimize the time between the moment of SCA and the start of cardiopulmonary resuscitation (CPR) and cardiac life support. This can be achieved by a witness or bystander who first has to alarm the emergency medical system and who starts with CPR immediately thereafter.
An increase in resuscitation success rate was observed over time. Although we could not find any differences in success related factors such as bystander CPR or time delay over time, other factors may have played a role. A possible factor may be that since the end of 1993, all ambulances are equipped with portable defibrillators and portable apparature for monitoring rhythm and blood saturation. Furthermore at that time, all nurses and drivers had received a professional training in resuscitation.

Nowadays, as described in chapter 8, still many of those who witness SCA do not start basic CPR. In view of the fact that most SCAs occur at home and that people with a history of cardiac disease have a higher chance of dying suddenly, particular attention should be given to the training of family members, especially the spouses and partners of cardiac patients. In a number of studies mouth to mouth ventilation and cardiac massage have been proven to be techniques which can be easily applied by lay people (21,22). Although the immediate application of adequate basic CPR and/or advanced life support is the only way to survive SCA in the majority of victims, we have to realize that there is still a small group of victims who a priori will not benefit from it. These are victims in whom the cause of SCA is for example aortic rupture.
According to our and other studies, probably the best chance to survive SCA have those victims who have no previous cardiac history, who have a cardiac cause of SCA, in whom VT or VF is the mechanism of SCA, who are witnessed, who are not at home, and who are resuscitated immediately by a witness and/or the EMS.

In this study it was shown that most of the SCA victims could not have been identified long before the event. It is therefore suggested that prevention has to be focussed on preventing the occurrence and progression of coronary artery disease by identifying and controlling risk factors in people without CHD and in those known with CHD.
In 1998 a regional prevention project will be started in the region of Maastricht by the Public Health Service in cooperation with the department of Cardiology and other groups of the University of Maastricht. The aim of this project is to identify and reduce risk factors in both patients who are known with CHD and those who are not known with CHD by counseling by a prevention consultant. Furthermore education programs will be started in the community to make the general population aware of the risks of certain risk and life-style factors (smoking, diet, physical activity) and to help them to control these factors.
Also it is important to give more attention to educate, especially the population not known with heart disease, how to recognize symptoms of an acute myocardial infarction and to instruct them to call an ambulance immediately. This requires continuous education.
Particular attention should be given to the training in resuscitation techniques of laymen and especially family members of patients with heart disease. In october 1992 the department of Cardiology started together with the Public Health Service a resuscitation program especially for family members of patients with CHD.
Finally, new telecommunication methods should be developed to alarm health workers to locate and provide CPR for people who live alone.

To evaluate the value of prevention measures, the incidence and the survival rate, the SCA registry should be continued in the coming years. To compare our results with incidence and survival rates in other communities, it is important that future studies use the same inclusion criteria and definitions for SCA.

REFERENCES

1. Commissie van de Gezondheidsraad. Gezondheidsraad advies inzake epidemiologie en preventie van ischemische hartziekten. No 1984/16, Den Haag, 29 juni 1984.
2. WHO MONICA project. MONICA, revised edition. Geneva cardiovascular research unit. WHO;1990.
3. Hunink MGM, Goldman L, Tosteson ANA, et al. The recent decline in mortality from coronary heart disease, 1980 - 1990: The effect of secular trends in risk factors and treatment. JAMA 1997;277:535-42.
4. Weijenberg M. Prospective studies on coronary heart disease in the elderly. The role of classical and new risk factors. Landbouwuniversiteit Wageningen 1996 (thesis).

5. Doll R, Peto R. Mortality in relation to smoking: 20 years observation of male British doctors. Br Med J 1976;11:1525-36.
6. Cummins RO, Ornato JP, Thies WH, et al. Improving survival from sudden cardiac arrest: The 'chain of survival' concept. A statement for health professionals from the advanced cardiac life support subcommittee and the emergency cardiac care committee, American Heart Association. Circulation 1991;83:1832-47.
7. Feinstein AR, Sosin DM, Wells CK. The Will Rogers Phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med 1985;312:1604-8.
8. Becker LB, Smith DW, Rhodes KV. Incidence of cardiac arrest: a neglected factor in evaluating survival rates. Ann Emerg Med 1993;22:86-91.
9. Kannel WB, McGee DL. Epidemiology of sudden death: insights from the Framingham study. Cardiovasc Clin 1985;15:93-105.
10. Wellens HJJ, de Vreede J, APM Gorgels. Sudden cardiac death. How to reduce the number of victims? Eur Heart J 1995;16(G):7-9.
11. Weld FM, Chu KL, Bigger JT Jr, Rolnitzky LM. Risk stratification with low-level exercise testing 2 weeks after acute myocardial infarction. Circulation 1981;64:250-8.
12. Sanz G, Castaner A, Betriu A, et.al. Determinants of prognosis in survivors of myocardial infarction. A prospective clinical angiographic study. N Engl J Med 1982;306:1065-70.
13. Kuchar DL, Thornburn CW, Sammel NL. Prediction of serious arrhythmic events after myocardial infarction. Signal averaged electrocardiogram, Holter monitoring and radio-nuclide ventriculography. J Am Coll Cardiol 1987;9:531-8.
14. Wellens HJJ, de Vreede J, Gorgels APM. Sudden cardiac death: A continuing challenge. In: Atrial and Ventricular Fibrillation: Mechanisms and Device Therapy. Allessie MA, Fromer M. Bakken Research Center Series volume 9, Futura Publishing Company, Inc., New York, USA 1997.
15. Wellens HJJ. Key references on sudden death:1980-1994. Circulation 1994;90:2547-53.
16. Bigger JT Jr, Fleiss JL, Kleiger R, et al. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation 1984;69:250-8.
17. Echt DS, Liebson PR, Mitchell B, et al. Mortality and morbidity in patients receiving encainide, flecainide or placebo: the Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991;324:781-8.
18. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;27:335-71.
19. Demirovic J, Myerburg RJ. Epidemiology of sudden coronary death: an overview. Prog Cardiovasc Dis 1994;37:39-48.
20. Oliver MF. Lack of impact of prevention on sudden cardiac death. J Am Coll Cardiol 1985;5/6:150B-154B.
21. Dracup K, Heaney DM, Taylor SE, Guzy PM, Breu C. Can family members of high risk patients learn cardiopulmonary resuscitation? Arch Intern Med 1989;149:61-4.
22. Van Kerschauer E, Delooz HH, Moens GFG. The effectiveness of repeated cardiopulmonary resuscitation in a school population. Resuscitation 1989;17:211-22.

SUMMARY

Part I

A meta-analysis on the prognosis after acute MI showed that in-hospital mortality decreased since the 1960s. The average in-hospital mortality was 29% during the 1960s, declining to 21% in the 1970s and 16% in the 1980s. Five year prognosis after discharge remained unchanged and was 33% in both the 1960s and 1970s.
In the population of the region of Maastricht, the incidence of MI remained the same during the study years. Of importance are the changes in patient characteristics over the years. In recent years the mean age of the infarct population increased (there was an increase in the age group over eighty), also more women experienced acute MI. Smoking habits decreased. A significant decrease in hospital mortality was observed between the early and late 1980s from 17% to 10%, staying the same in the 1990s. In-hospital mortality of patients admitted in 1994 was 9%. When comparing one year mortality in patients with acute MI admitted in the years 1982, 1988 and 1994, no change was observed. However, despite the fact that the 1 year mortality remained the same, patients admitted in recent years do better after discharge in terms of anginal complaints, reinfarctions and readmissions. After 2.5 years survival curves start to diverge for patients admitted in the early and late 1980s with a better 5-year outcome for the latter group. 5-year mortality of patients discharged in 1982 was 29% and 19% for those discharged in 1988. There seems to be a trend towards a shift in cause of mortality from arrhythmic to pump-failure.
The importance of left ventricular dysfunction as a determinant of survival after MI is well recognized and also in our study the most consistent variable related to death after MI appeared to be any sign of diminished left ventricular function. Furthermore, age above 70 and ventricular arrhythmias were associated with mortality after MI.
Hospital mortality from UAP was low and no change was found in mortality for patients admitted in the 1980s or 1990s. Also one year mortality figures after discharge remained unchanged.
However also for patients with UAP, survival curves diverged and a significant lower late mortality was found for those admitted in the late 1980s; 25% versus 15%. Also in these patients signs of left ventricular dysfunction were associated with mortality.
A subanalysis was performed in patients presenting with UAP who later appeared to have an MI on the basis of subsequent cardiac enzymes. In this group mortality was the same as in the group were the diagnose remained

unstable angina, although morbidity in terms of readmissions and functional class of angina was worse.

Part II

The overall yearly incidence of out-of-hospital SCA in the Maastricht area appeared to be 1/1000 inhabitants in the age category 20 to 75 years and did not change significantly during a period of five years (1991-1995).
SCA mainly occurred at home and 40% was unwitnessed. Seven percent of all SCA victims left the hospital alive after successful resuscitation. The percentage of survival in witnessed SCA at home being lower compared to outside (8% versus 18%).
44% Of men and 53% of women were unknown with heart disease and therefore could not have been identified before the event. It was estimated that victims known with a cardiac disease had about an eleven times higher risk of SCA compared to those not known with heart disease. Most of these latter victims had CHD and a previous MI. The mean time interval between previous MI and SCA was 6,5 years. However the number of SCA victims with a previous MI decreased from 43% in 1991 to 31% in 1994. A poor left ventricular function, which has been identified as an important predictor for SCA after acute MI by many studies, was present in less than half of these latter patients. Unfortunately, the majority of SCA victims could not have been identified as being at high risk before the event.
In patients with coronary artery disease, a previous myocardial infarction, hypertension and diabetes mellitus are independent risk indicators for SCA while life-style factors such as heavy coffee drinking and moderate alcohol consumption were respectively negatively and positively associated with survival from SCA.
Autopsy findings showed that a non-cardiac cause of SCA was present in 24%: in 6% of those with and in 38% of those without known heart disease. Pulmonary embolism and aortic disease were the most important non-cardiac causes. Coronary artery disease was the most common finding in all sudden cardiac death victims (98%). A healed MI was found in 75% of those with and in 33% of those without a previous cardiac history. Between the two groups there was no difference in the severity of disease in the coronary vessels. A recent MI was demonstrated in 58.5% of the sudden coronary death victims; in 52% of those with and in 65% of those without known cardiac disease.
Of all SCA victims in whom resuscitation was attempted by the ambulance personnel during a five year period, 16% were discharged alive from hospital. Resuscitation success rate increased significantly from 12% in 1991 to 25% in 1995. In all but one survivor of SCA a cardiac cause for SCA was diagnosed.

An acute MI was diagnosed in 51% of the survivors; in 32% of those with and in 68% of those without a previous cardiac history.
Negatively associated with survival from SCA in victims who were resuscitated by the ambulance personnel was the presence of a previous cardiac history. Factors independently positively associated with survival were a delay time between the moment of collapse and the start of resuscitation of less than 4 minutes, an ambulance delay time of less than 8 minutes and VT or VF as the first documented rhythm by the ambulance personnel.

NEDERLANDSE SAMENVATTING

Deel 1

Tot de acute vormen van het coronarialijden (kransslagaderlijden) behoren: het acute hartinfarct (veroorzaakt door een totale afsluiting van een kransslagader, meestal door een stolsel), instabiele angina pectoris (ten gevolge van een ernstige vernauwing van een kransslagader) en de plotselinge hartdood.
In de geïndustrialiseerde landen zijn deze uitingen van coronarialijden nog steeds de belangrijkste doodsoorzaak. Tot aan het einde van de 50-er jaren was er een toename van het overlijden aan coronarialijden. Na een afvlakking in de jaren 60 is sinds 1970 in Nederland een geleidelijke daling opgetreden.
De afname van het aantal overledenen kan het gevolg zijn van het feit dat de ziekte minder voorkomt of milder verloopt. Indien dit zo is dan ligt waarschijnlijk een afname van de factoren die het risico op hart- en vaatziekten vergroten hieraan ten grondslag. Een andere (minder waarschijnlijke) verklaring kan zijn dat er een toename van andere doodsoorzaken is opgetreden. Een derde mogelijkheid is dat de behandeling van het hartinfarct en van de instabiele angina pectoris in de loop der jaren is verbeterd. Dit laatste wordt gesuggereerd door een analyse van de wereldliteratuur naar de verandering in de percentages overledenen aan een hartinfarct. Uit deze studie blijkt dat de vooruitzichten op korte termijn verbeterd zijn maar een verbetering van de lange termijn prognose kon niet worden aangetoond, mogelijk door gebrek aan voldoende studies op dat gebied.
Om beter ingelicht te zijn over de korte- en lange termijn prognose in de regio van het Academisch Ziekenhuis Maastricht, werd een onderzoek uitgevoerd bij de patiënten van de regio zuidelijk Zuid-Limburg die in de jaren 1982, 1988 en 1994 in het ziekenhuis werden opgenomen met een van de acute vormen van het coronarialijden.
Het onderzoek is uniek omdat zonder selectie naar leeftijd alle patiënten die in het ziekenhuis waren opgenomen met een acuut kransslagaderlijden konden worden vervolgd.
Een van onze bevindingen was dat de leeftijd waarop mensen een infarct kregen tussen 1988 en 1994 duidelijk was toegenomen. Ook waren de laatste jaren vrouwen vaker het slachtoffer. Verder zagen we dat het roken (de belangrijkste beïnvloedbare risicofactor) in de laatste jaren is afgenomen.
Een belangrijke bevinding was dat de kans op overlijden in het ziekenhuis als gevolg van een hartinfarct tussen 1982 en 1988 duidelijk afnam. Daarna is het sterftecijfer gestabiliseerd en bleken in 1994 evenveel mensen in het ziekenhuis aan een hartinfarct te zijn overleden als in 1988.

De oorzaak van de forse daling tussen 1982 en 1988 is ondermeer gelegen in het feit dat patiënten in 1988 veel agressiever werden behandeld. Er werd namelijk maximaal gebruik gemaakt van nieuwe behandelingsmethoden die als doel hebben de afgesloten of ernstig vernauwde kransslagader zo snel mogelijk open te maken zodat de bloedstroom naar de bedreigde hartspier zich kan herstellen. Voorbeelden van deze technieken zijn: het toedienen van een stolseloplossend middel (thrombolyticum) en de Dotter-behandeling (PTCA) waarbij met een ballonnetje de afsluiting en de vernauwing worden opgeheven. Het bleek ook zo te zijn dat patiënten die meerdere vernauwingen in de kransslagaders hadden (met als risico een totale afsluiting); veel frequenter een kransslagader-omleidingsoperatie ondergingen (CABG). Verder werd aangetoond dat de hartinfarctpatiënten die in 1988 en 1994 opgenomen werden, eerder na het begin van de klachten in het ziekenhuis arriveerden dan de patiënten opgenomen in 1982. Hierdoor nam de overlevingskans toe en werd het hartinfarct in grootte beperkt. Het is nu zelfs zo dat wanneer de patiënt met een hartinfarct zo snel mogelijk in het ziekenhuis komt en behandeld wordt, er vaak nauwelijks aantoonbare schade aan de hartspier optreedt.
Verder toonde de studie aan dat de kans op overlijden binnen een jaar na ontslag uit het ziekenhuis gelijk was voor de patiënten opgenomen in respectievelijk 1982, 1988 en 1994. Opvallend is echter dat rond 2.5 jaar na ontslag een verschil zichtbaar werd in de overlijdenskans tussen de patiënten opgenomen in 1982 en 1988; dit verschil was zichtbaar tot minimaal 5 jaar na ontslag. Naast de genoemde daling in overlijdenskans bleek ook dat de patiënten van 1988 en 1994 veel minder chronische hartklachten ontwikkelden hetgeen ook een belangrijk winstpunt is. Dit laatste is niet alleen het gevolg van de verbeterde behandeling in de acute fase maar ook het gevolg van betere medicijnen die de laatste jaren zijn ontwikkeld om de gevolgen van een hartinfarct te beperken en het risico op een nieuwe gebeurtenis te verminderen. Voorbeelden hiervan zijn medicijnen die de bloeddruk verlagen, medicijnen die het cholesterol verlagen en medicijnen die de bloedstolling beïnvloeden. Ofschoon aan deze nieuwe medicijnen en behandelingsmethoden meer kosten verbonden zijn, werden patiënten die in 1988 en 1994 een infarct kregen minder vaak opgenomen in de daaropvolgende jaren hetgeen waarschijnlijk een duidelijke kostenbesparing betekende.
De kans om in het ziekenhuis te overlijden aan instabiele angina pectoris (ernstig vernauwde/bijna dichte kransslagader) is gering en derhalve kon een daling van de sterfte aan dit ziektebeeld niet worden aangetoond in de door ons onderzochte jaren. Belangrijk is hierbij dat de patiënten van 1988 ook weer minder chronische hartklachten ontwikkelden. Verder hebben wij gevonden dat ook gedurende een follow-up van vijf jaar de kans op overlijden duidelijk verminderde voor de patiënten van 1988, waarschijnlijk door de veel intensievere behandeling, gericht op het herstellen van de

bloedstroom in de kransslagaders en mogelijk ook door het verminderen van de risicofactoren.
Hoewel gebleken is dat in de onderzochte jaren het totale aantal patiënten met een hartinfarct of instabiele angina pectoris gelijk is gebleven werd het aantal patiënten in de leeftijdscategorie onder de 70 jaar kleiner. Er treed dus een verschuiving op van deze ziektebeelden naar een oudere leeftijd. Voor de toekomst is het dan ook van groot belang om ons niet alleen te richten op de behandeling van de verschillende vormen van kransslagaderlijden maar ook na te gaan of preventieve maatregelen het mogelijk maken de ziekte te voorkomen. Om dit zeker te kunnen weten is ook in de komende jaren nauwkeurige registratie van voorkomen en gevolgen van coronarialijden noodzakelijk.

Deel 2

In Nederland sterven jaarlijks nog steeds veel mensen plotseling buiten het ziekenhuis aan een acute hartaandoening. Dit plotseling overlijden van een persoon in de bloei van zijn leven is een dramatische gebeurtenis. Nauwkeurige gegevens over de omvang van dit probleem in Nederland ontbreken. Vandaar dat wij dit in de periode 1991 tot en met 1995 zorgvuldig in onze regio zijn nagegaan. Uit ons onderzoek bleek dat in de regio zuidelijk Zuid-Limburg jaarlijks 1/1000 inwoners in de leeftijdscategorie 20-75 jaar plotseling overlijdt, hetgeen bijna een vijfde van de totale sterfte is in deze leeftijds-categorie.
Naast de incidentie van dit probleem zijn wij de omstandigheden nagegaan waaronder zich een acute hartstilstand voordoet. Het bleek dat bij zes van de tien mensen die een hartstilstand kregen een getuige aanwezig was en dat acht van de tien mensen thuis waren op het moment van de hartstilstand.
Een acute hartstilstand kan zich voordoen bij patiënten die bekend zijn met een hartziekte maar ook bij ogenschijnlijk 'gezonde' personen. Zo bleek dat 4 van de 10 mannen en 5 van de 10 vrouwen die een hartstilstand kregen niet bekend waren als hartpatiënt. Echter, hartpatiënten bleken een 11 keer zo grote kans te hebben op een acute hartstilstand dan mensen die niet bekend waren als hartpatiënt. De meeste slachtoffers die bekend waren bij de cardioloog of de huisarts met hartklachten hadden in het verleden een of meerdere hartinfarcten doorgemaakt. Het gemiddelde aantal jaren tussen het hartinfarct en de plotse hartstilstand was 6,5 jaar. Bij patiënten die bekend waren met een vroeger doorgemaakt hartinfarct was een slechte functie van de linker hartkamer, hetgeen beschouwd wordt als een voorspeller van een acute hartstilstand, aanwezig bij minder dan de helft. Het merendeel van de slachtoffers kon dus van te voren niet worden herkend als mensen met een groot risico op een acute hartstilstand.

Uit onderzoek naar risicofactoren voor een acute hartstilstand bij patiënten die bekend zijn met ziekte van de kransslagaders bleek dat een hartinfarct in de voorgeschiedenis, hoge bloeddruk en diabetes mellitus belangrijke risicofactoren zijn voor het krijgen van een hartstilstand. Ook beïnvloedbare factoren zoals koffie- en alcoholconsumptie lijken van belang. Uit ons onderzoek bleek, dat het drinken van meer dan 10 kopjes koffie per dag een verhoogd risico geeft op het krijgen van een acute hartstilstand bij patiënten bekend met ziekte van de kransslagaders. Daarentegen liet het drinken van gemiddeld 1 tot 21 glazen alcoholische drankjes per week een beschermend effect zien.
Na toestemming van de familie om de oorzaak van het plotse overlijden te bestuderen, werd bij een vierde van de slachtoffers een obductie (lijkschouwing) uitgevoerd. Bij drie vierde van deze groep bleek dat de hartstilstand veroorzaakt was door een hartaandoening; voornamelijk door ziekte van de kransslagaders. De meest voorkomende niet cardiale oorzaken waren een longembolie en een scheur in de lichaamsslagader (dissectie van de aorta). Een niet cardiale oorzaak werd vaker gevonden bij slachtoffers die niet bekend waren als hartpatiënt (38%) dan bij diegenen die wel bekend waren als hartpatiënt (6%). Een vroeger doorgemaakt hartinfarct was te zien bij drie vierde van de slachtoffers die bekend waren als hartpatiënt en bij een derde van de slachtoffers die niet bekend waren als hartpatiënt. Bij deze laatste groep is het hartinfarct dus niet gevoeld of herkend. Een recent hartinfarct werd gevonden bij 52% van de slachtoffers die bekend waren als hartpatiënt en bij 65% van de slachtoffers die niet bekend waren als hartpatiënt.
De enige kans om een hartstilstand te overleven is door middel van snelle uitvoering van een aantal stappen. 1) het vaststellen van de circulatiestilstand en het alarmeren van de ambulancedienst 2) het beginnen met hartmassage en mond op mond beademing, 3) het vaststellen van de oorzaak van de circulatiestilstand en het normaliseren van het hartritme, 4) het in stand houden van het hartritme en vervoer naar de cardiologische afdeling van het ziekenhuis voor verdere diagnostiek en behandeling. Stap 1 moet worden gezet door mensen die bij het optreden van de circulatiestilstand aanwezig zijn, zoals familieleden of bekenden of (zoals op straat) door onbekende getuigen. Na het bellen van 06-11 (momenteel 112) is zo snel mogelijk het in reanimatie getrainde ambulancepersoneel aanwezig. Deze nemen de hartmassage en beademing over en corrigeren de hartritmeafwijking. Vaak is de hartritmeafwijking kamerfibrilleren waardoor bij het chaotische ritme het hart niet meer in staat is bloed door de bloedvaten te pompen. Om kamerfibrilleren te beëindigen moet een krachtige stroomstoot (met behulp van een defibrillator) aan het hart worden toegediend. Wanneer het hartritme is hersteld wordt de patiënt voor verdere behandeling naar het ziekenhuis vervoerd.
In de periode 1991 tot en met 1995 heeft 16% van alle slachtoffers, waarbij een reanimatiepoging werd ondernomen door de ambulanceverpleegkundi-

gen, het ziekenhuis levend verlaten. Het succespercentage steeg van 12% in 1991 naar 25% in 1995. Een mogelijke oorzaak voor deze stijging is het feit dat vanaf eind 1993 alle ambulances voorzien waren van draagbare apparatuur voor het registreren en het beëindigen van het chaotische hartritme (kamerfibrilleren) dat bij veel slachtoffers wordt aangetroffen. Daarnaast heeft het ambulancepersoneel eind tachtiger en begin negentiger jaren zowel een basis- als ook nascholings-cursussen gevolgd waarbij de reanimatietechnieken uitvoerig zijn behandeld.
Het succes van een reanimatiepoging wordt bepaald door een aantal van elkaar onafhankelijke factoren. Uit het onderzoek bleek dat het starten van een reanimatiepoging binnen 4 minuten, het aanwezig zijn van een ambulance binnen 8 minuten en het aantreffen van een zeer snel of chaotisch hartritme (kamerfibrilleren) bij de patiënt het overleven gunstig beïnvloedden. De kans op succes van de reanimatie was groter indien de patiënt vóór de circulatiestilstand niet bekend was met hartklachten.
Een acuut hartinfarct als oorzaak van de hartstilstand werd gevonden in de helft van de ziekenhuisoverlevenden. Het lijkt dus van belang om door middel van voorlichting nog meer aandacht te besteden aan het herkennen van de symptomen en klachten die zich kunnen voordoen bij een hartinfarct. Het feit dat een hartstilstand zich meestal thuis voordoet en vaak een familielid hiervan getuige is onderstreept het belang van het volgen van reanimatiecursussen door leken. Daar hartpatiënten een grotere kans hebben op een hartstilstand, zijn juist familieleden van hartpatiënten een duidelijke en herkenbare doelgroep voor deelname aan reanimatiecursussen.

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